THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

I. A SEARCH FOR THREE-CENTER NONCLASSICAL CARBANIONS: AMINE ANALOGUES

II. ANOMOLOUS LITHIUM ALUMINUM HYDRIDE REDUCTION OF CARBON-CARBON DOUBLE BONDS IN 7-AZABICYCLO[2.2.1]-HEPTENYL SYSTEMS

III. ANGULAR DEPENDENCE OF VICINAL ^{14}N-H COUPLING CONSTANTS IN BICYCLIC AMMONIUM SALTS

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APPROVED BY

DISSERTATION COMMITTEE

Dedication

Dedicated to the memory of those who died at Kent State, and in Vietnam. The author sincerely hopes that none were in vain.

ACKNOWLEDGMENTS

The author wishes to thank first my parents who provided both the background and continuing support that made this study possible. Dr. Alan P. Marchand is to be especially thanked, not only as an educator, but as the person most responsible for my entrance to graduate school. The author is most thankful to my peers who provided assistance, both academic and social. Notable thanks go to my friend and associate J. Mike Wilson, for our numerous and productive late night discussions. Finally, the author must acknowledge the influence of the social milieu of the university community during the late 60's and early 70's.

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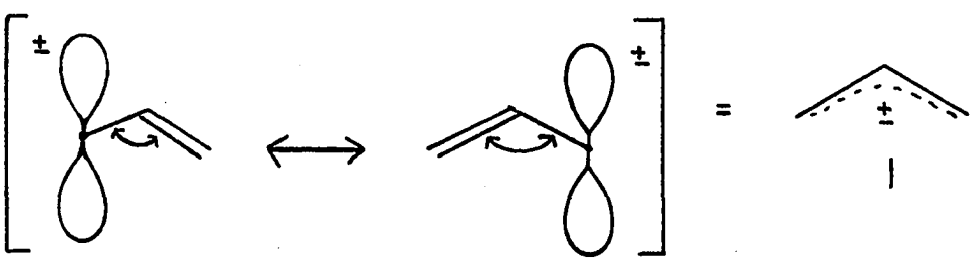
Part I

I. A SEARCH FOR THREE-CENTER NON-CLASSICAL CARBANIONS; AMINE ANALOGUES

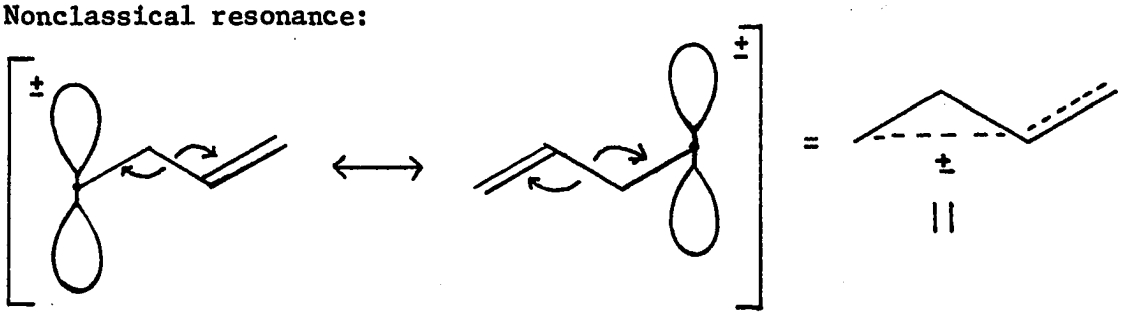
INTRODUCTION

The concept of the nonclassical ion has fostered considerable research effort and no small amount of controversy. Whereas classical resonance-stabilized ions involve continuous overlap across a σ-bonded framework, (I), stabilization of nonclassical ions is derived from significant 1,3-overlap which is usually intermediate between σ and π bonding. (II)

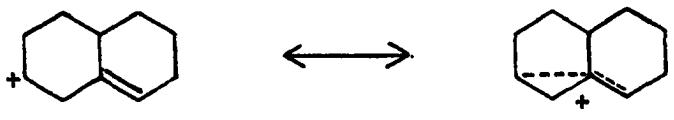
Classical resonance:



Nonclassical resonance:



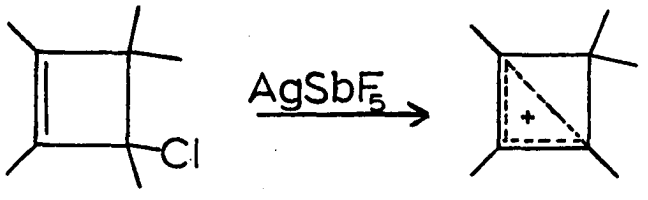
Although nonclassical ions are generally carbocyclic, the well known ion intermediate obtained by addition of Br_2 to olefins (the bromonium ion) was actually the first "nonclassical" ion.[1-4] This was followed in 1948 by Winstein's introduction of the term "nonclassical participation" to explain the rapid exchange and enhanced solvolytic rates in the now famous cholesteryl:i-cholesteryl derivatives.[5-7]



Winstein's research indicated for the first time that remote π-orbitals could significantly participate in the stabilization of an incipient ion. These studies led to the adoption of the terms "homoallylic", and, more generally, "homoconjugation".[8] The next logical extension of these concepts followed several years later with the introduction of the term "homoaromaticity".[9] Aromaticity as defined by Hükel molecular orbital (HMO) theory[10] requires the continuous overlap of a (4n+2) π electron cycle. In fact, one of the basic assumptions in this theory is that $\beta_{i,j}=0$ for atoms i,j not directly bonded, (i.e., it is assumed that resonance between non-bonded atoms is vanishingly small). Homoaromaticity encompasses those cases where continuous, cyclic electron delocalization occurs with interruptions of the σ-framework. More specifically, mono, -bis, -tris, -... perhomoaromaticity[11] refers to situations where there are one, two, three, ...n, interruptions of the σ framework, respectively.

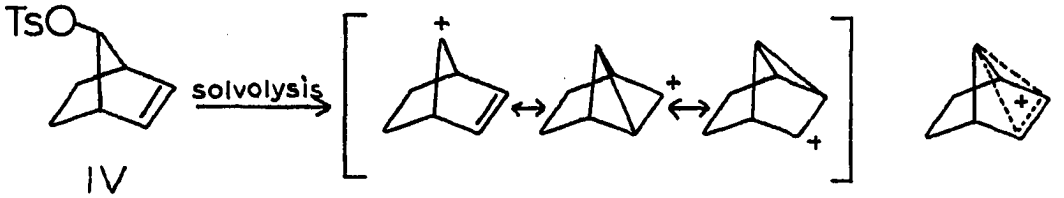
Evidence for the simplest homoaromatic ion (monohomo-) was

derived via observation of UV spectra of the cyclobutenium ion III. Katz and co-workers[12] noted that absorption by this ion was at a wavelength intermediate between simple allylic cations and the cyclopropenyl cation.



III

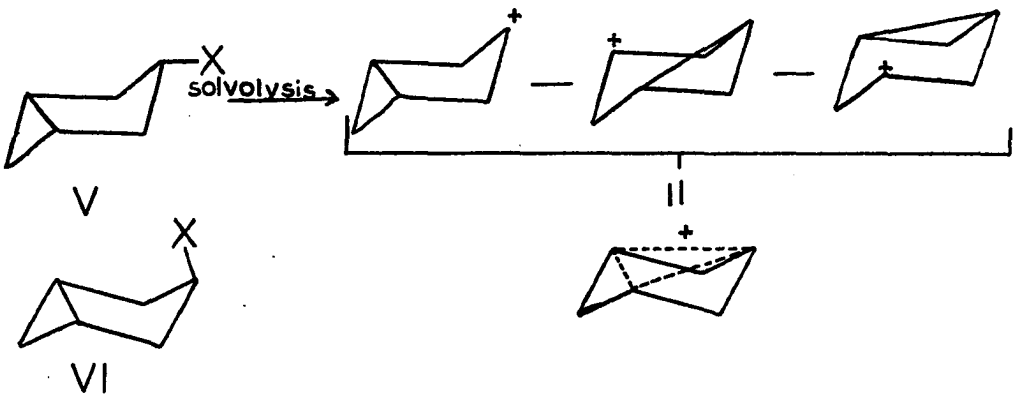
Comparison of the rates of solvolysis of anti-7-substituted norbornenes relative to those for the corresponding 7-substiuted norbornanes suggests the importance of bishomoaromatic stabilization in the former system:



IV

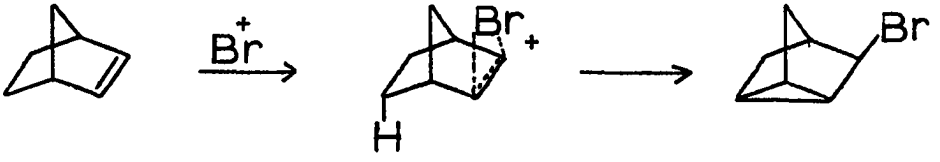
Solvolysis of IV occurs some 100 billion times (10^{11}) faster than does solvolysis of the corresponding 7-substituted norbornane.[13]

Trishomoaromaticity[14] is apparent in the solvolysis rate of V, which is some35 times faster than the cis isomer, VI.

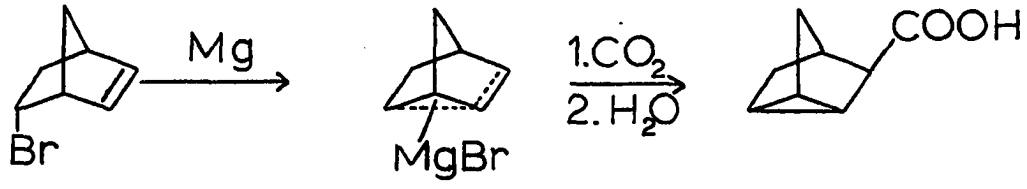


Proof of (or even postulation of) nonclassical carbanion intermediates is far more scarce than is the case with nonclassical carbonium ions. This is clearly pointed out by Bartlett's collection of papers[8] on nonclassical ions. Of the 75 papers included, not one concerns a nonclassical carbanion, even though a homoallylic carbanion was suggested as a possible intermediate as early as 1950.

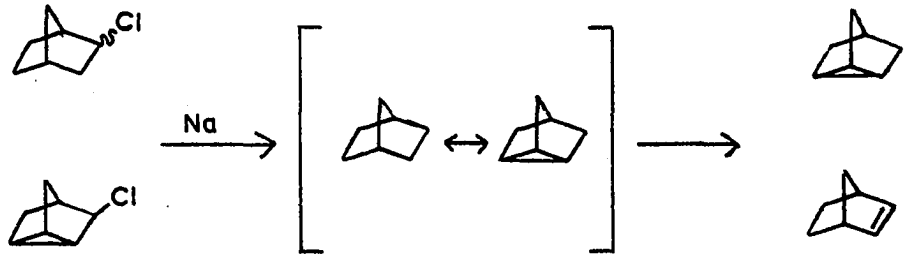
Roberts and co-workers[15] examined the reaction of norbornene with N-bromosuccinimide, and found that the major product was nortricyclyl bromide. It was suggested that initial formation of the bromonium ion was followed by base abstraction of a proton from the 5-position and subsequent homo-elimination.



It was also reported that treatment of endo-5-norbornenylmagnesium bromide resulted in the formation of nortricyclanecarboxylic acid as the only product. This facile homoallylic rearrangement of a Grignard reagent could involve a nonclassical carbanion.



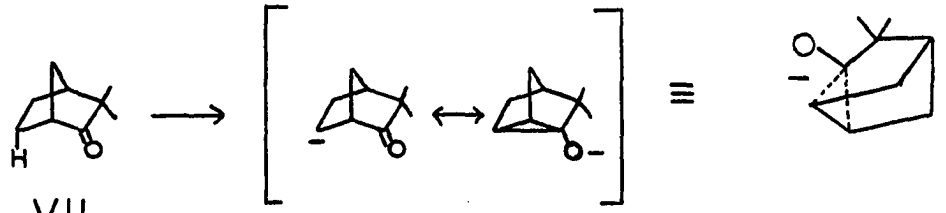
In a similar reaction,[16] treatment of both nortricyclyl chloride and 5-chloronorborn-2-ene with sodium metal, yielded after quenching, approximately the same mixture of nortricyclene and norbornene, the former being the major product.



The intermediate common to both starting materials can be represented as a nonclassical carbanion, or, instead, as a rapidily equilibrating pair of classical carbanions.[17] Similar results were obtained in other studies involving generation of a carbanion intermediate in norbornene and

norbornadiene.[18]

A nonclassical enolate anion has been cited as a possible intermediate in the base catalyzed racemization of camphenilone,[19] VII. Treatment of VII with potassium t-butoxide results in complete racemization. This is suggested to occur via the symmetric homoenolate, protonation of which yields racemized VII.



VII

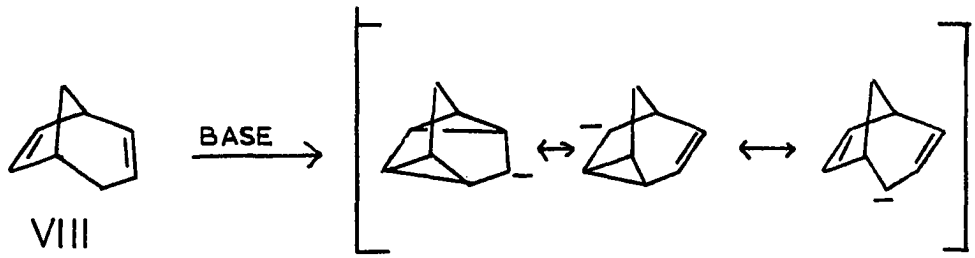
Other homoenolate intermediates have been discussed by Nickon and coworkers.[20]

The first cyclic nonclassical carbanion[21] was suggested to account for large differences between the rates of H-D exchange in bicyclo(3.2.1)octa-2,6-diene (VIII) and bicylo(3.3.1)oct-2-ene, (IX).

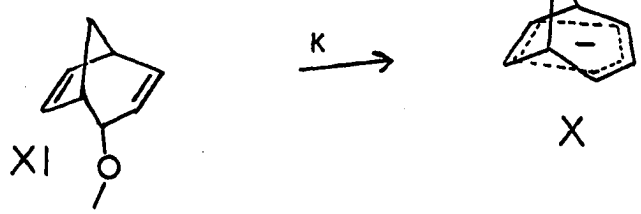
VIII IX

$$\frac{k_{VIII}}{k_{IX}} = 3 \times 10^4$$

The rate acceleration of VIII relative to IX was attributed to the resonance stabilized bishomocyclopentadienyl carbanion, X.



VIII

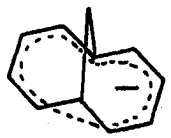


XI

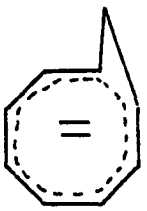
X

The proton nmr spectrum of X was observed[22] for the species formed by potassium metal cleavage of 2-methoxy bicyclo(3.3.1)-octa-3, 6-diene,(XI). In the nmr spectrum of this species, the aromatic ring protons were shifted ca. 2.5 ppm upfield, bridgehead protons shifted ca. 0.1 ppm upfield and bridge protons ca. 1.15 ppm upfield, relative to the nmr spectrum of VIII. The upfield shift of the aromatic protons was due to the negative charge density, (protons bonded to carbons which have carbanion character are shielded by the large electron density) but the upfield shift of the bridge protons was due to their position in the shielding region of the ring current. The parent hydrocarbon (VIII) is formed when X, formed by potassium metal cleavage of XI, is quenched. However, equilibration of VIII with Streitwieser's catalyst (cesium cyclohexylamide in cyclohexylamine) followed by quenching, affords a

mixture of bicyclic, tricyclic, and tetracyclic hydrocarbons. These latter three products can be thought of as arising via quenching of X through each of its three resonance forms, as indicated above.

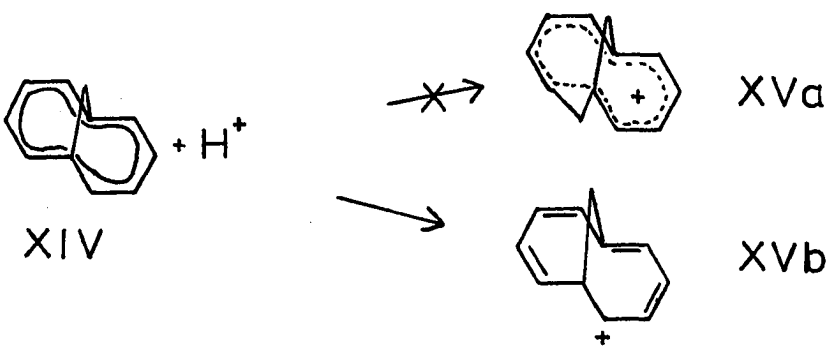


XII



XIII

Two 10-electron homoaromatic nonclassical carbanions, XII and XIII, have been reported in the literature.[23,24] In both cases, aromaticity was suggested by features of their respective proton nmr spectra. Deshielding of the ring protons was not observed because of the greater shielding effect of negative charge density. However, protons above the plane of the ring, where there is little negative charge density, were shifted upfield. This shielding must be a result of an induced paramagnetic field, and, hence, it was concluded that an aromatic ring current was present.



Just as homoaromaticity is stabilizing, Breslow[25] suggested that homoantiaromaticity should be destabilizing. With this in mind, Winstein and co-workers examined the proton nmr spectra of a potentially monhomoantiaromatic carbonium ion.[26] If protonation of 1,6-methanocyclodecapentaene (XIV) were to result in cyclic delocalization (1,9 overlap) of the 4n π electron system, XVa, the resulting species would be antiaromatic. The proton nmr spectra of the cation indicated that neither a paramagnetic[27] nor a diamagnetic[28] ring current were operative. Instead, the nmr spectrum was thought to be more consistent with structure XVb for the cation. Accordingly, the authors concluded that the ion was simply a classical carbonium ion.

As can be inferred from the previous example, methods based upon direct observation of homoantiaromatic species have an inherent problem which has limited such investigations. The problem is that direct observation of antiaromaticity is like looking at that which is not! Homoconjugation requires orbital overlap, but overlap in an antiaromatic species in unfavorable. The result is that antiaromaticity can only be inferred from the absence or retardation of any process which involves the unfavorable overlap.

Because of a dearth of information concerning homoantiaromaticity, the purpose of this investigation is to prepare and test various models that we hope will clearly indicate the <u>destabilizing</u> effect of homoantiaromaticity <u>vis-à-vis</u> the <u>stabilizing</u> effect of homoconjugation. Specifically, we intend to show that a <u>bis</u>homoconjugated anion in a symmetric 4 π electron system is unstable relative to an analogous homoallylic anion. The method of approach involves the preparation and

observation of inversion equilibria of several bicyclic amines which are isoconjugate and isoelectronic with bishomocyclopropenyl and homoallylic anions, respectively.

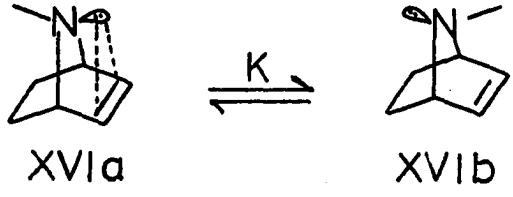
CHAPTER II

DISCUSSION

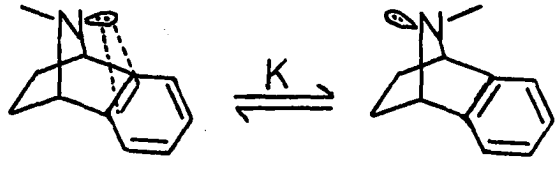
Observation of the effects of antiaromaticity is made difficult by its very nature. The equilibrium geometry of a neutral molecule, or even an incipient ion, is always that which is most stable. However, homoantiaromaticity should be destabilizing; accordingly, the geometry of the molecule or ion will be that which minimizes the destabilizing interaction. For example, consider a molecule with two interconvertable conformations, one of which is potentially antiaromatic. If the steric effects are the same in both conformations, then the conformation which is potentially antiaromatic will represent a smaller proportion of the mixture of the two.

In light of the above arguments, it would appear that the destabilizing effects of homoantiaromaticity can only be observed through judicious choice of a model system. This model system must be either sufficiently constrained so that destabilization can be observed in its formation or in its reactions, or it must be sufficiently mobile and well-defined so that the geometry of the equilibrium position will reflect specifically this destabilization. We have chosen to examine the thermodynamic stability of the invertomers of N-methyl-7--azanorbornene (XVI) and its benzo analogue XVII relative to that of N-methyl isoquinuclidine (XVIII) and its benzo analogue XIX. It is proposed that

the invertomer of XVI and XVII with the methyl group anti to the π system, XVIa and XVIIa, will be destabilized due to a bishomoantiaromatic interaction of the nitrogen lone pair. Hence, the equilibrium constant, K, for XVIa $\rightleftharpoons$ XVIb should be greater than one. (When the lone pair is syn to the ethylene bridge, the system is isoelectronic and isoconjugate with the cyclopropenyl carbanion).

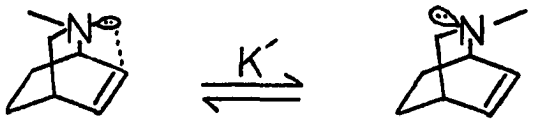


XVIa XVIb

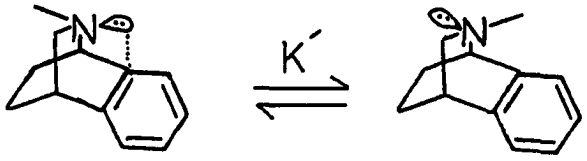


XVIIa XVIIb

Conversely, we expect preferential stabilization of invertomers XVIIIa and XIXa, due to the favorable interaction of the nitrogen lone pair with the π bond. Here, the equilibrium constant K' for XVIIIb $\rightleftharpoons$ XVIIIa should be less than one. Invertomer XVIIIa is isoelectronic and isoconjugate with an allyl anion.



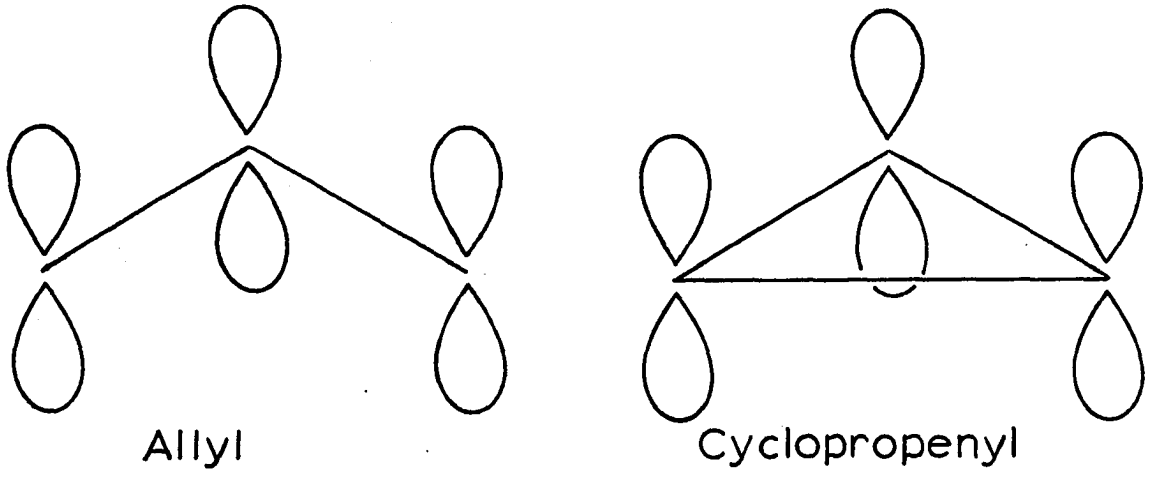
XVIIIa XVIIIb

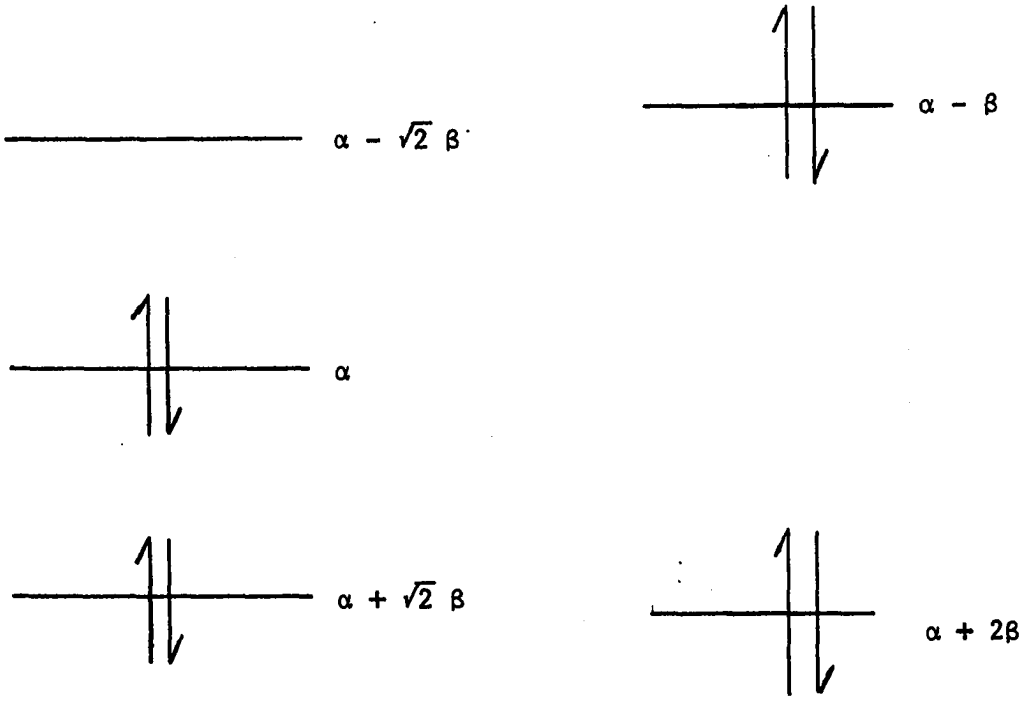


XIXa XIXb

The delocalization energies of cyclopropenyl and of allyl carbanions are depicted in Figure 1. Based on the usual definition of antiaromaticity[29] (less delocalization energy in cyclic model than in acyclic analogue) the cyclopropenyl anion is antiaromatic. As a first order approximation, we expect that our heterocyclic analogue of a bishomocyclopropenyl anion will also be antiaromatic.

Kinetic and thermodynamic confirmation of the expected antiaromatic destabilization of the cyclopropenyl carbanion has been obtained.[30] Studies examining the rate of H-D exchange of various cyclopropanes and cyclopropenes indicates the degree of antiaromatic destabilization which is present in anions derived from these systems. The rates of exchange of cyclopropane XX and methylenecyclopropane XXI are 10^4 and 10^8 times greater than that of cyclopropene XXII.





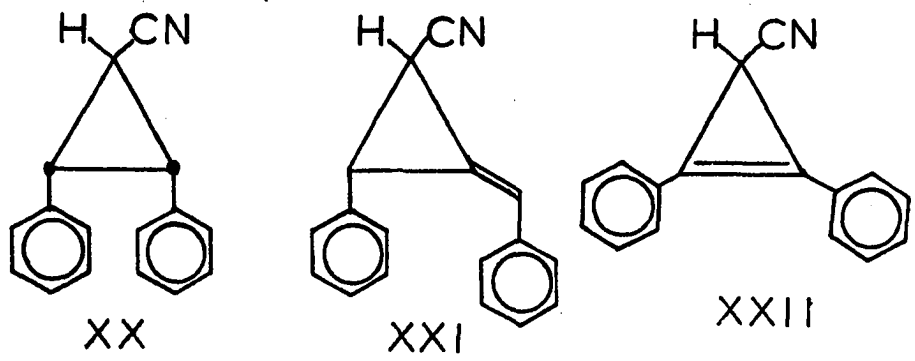
E_π(total) 4 α + 2.828β

DE_π = 0.828β

E_π(total) = 4 α + 2 β

DE_π = 0

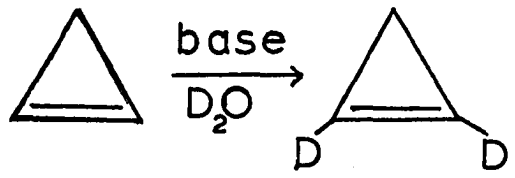
Figure 1. Simple Hückel M.O. calculation for allyl and cyclopropenyl carbanions[29]



XX XXI XXII

$$\frac{k_{XX}}{k_{XXII}} = 10^4 \qquad \frac{k_{XXI}}{k_{XXII}} = 10^8$$

Other evidence suggesting destabilization of the cyclopropenyl carbanion was obtained by Dorko and co-workers.[31] They noted that base catalysed H-D exchange occured exclusively between deuterated t-butyl alcohol and the olefinic protons in cyclopropene. Here, formation of a vinyl anion, the necessary intermediate in exchange, is less energetic than anion formation at the allylic position.



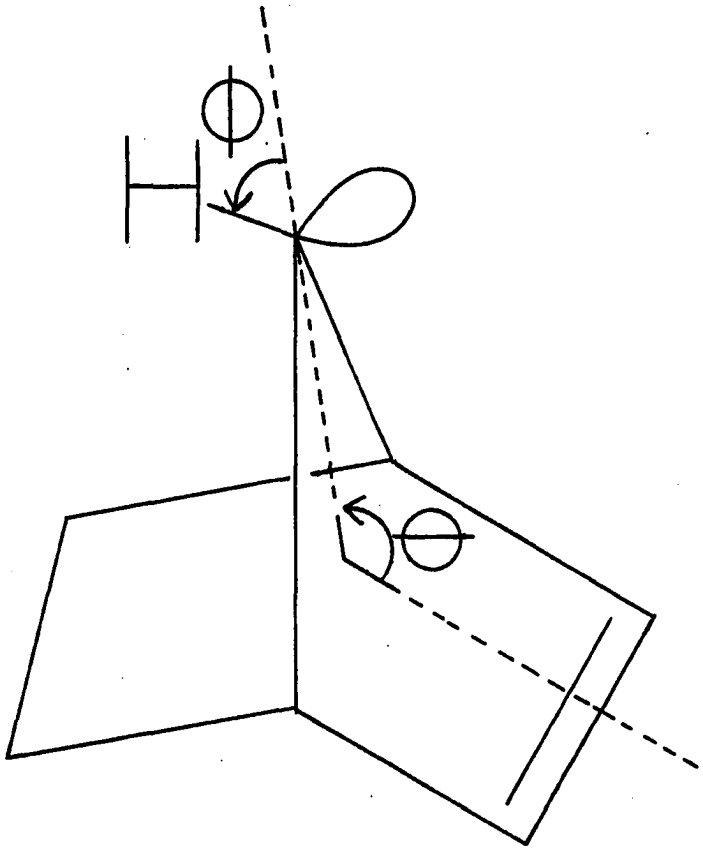
Thermodynamic evidence of antiaromaticity was obtained by Breslow by an electrochemical method. A difference of around 20 pK_a units between the acidity of 1,2,3- triphenylcyclopropene and that of

triphenylmethane was observed via examination of the electrochemical reduction of the corresponding carbonium ions.

$$ROH \overset{H^+}{\rightleftharpoons} R^+ \xrightarrow{+2e} R^-$$

There is some question, however, concerning the interpretation of the results. To generate an antiaromatic carbanion, one must start with an aromatic cation! [(4n+2) $\xrightarrow{-2e}$ 4n]. Therefore, it would seem that much of the measured energy went into destruction of the aromaticity of the carbonium ion. The relative proportions (destruction of aromaticity, creation of antiaromaticity) were not indicated. Evidence for antiaromaticity of other clasical systems (including carbonium ions, neutral molecules, and carbanions,) has been discussed by Breslow.[32]

Attempts to extrapolate the observed antiaromatic destabilization in classical ions to nonclassical models via computer simulation afforded equivocal results. Calculations were performed by Ohorodnyk and Santry[33] and by Dewar[34] on the geometry of the 7-norbornenyl cation, radical and anion. Both computer programs were designed to give the most stable geometry for the three species. (See Figure 2) Angle θ is formed by the intersection of the planes of the methylene and ethylene bridges. For the 7-cation, the magnitude is less than the magnitude of angle θ for norbornene (a decrease in θ brings the empty orbital on C_7 closer to the π bond resulting in more effective orbital overlap). This suggests that the vacant orbital at C_7 is stabilized by bishomoaromatic interaction. (vide supra) For the 7-anion, the magnitude of angle θ

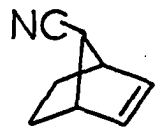


	NORBORNENE	CATION	ANION
Θ	92°	77°, 76.5°	124°, 122.5°
Φ	53°	16°, 12°	-22°, 58°

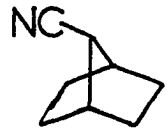
Figure 2. Computer calculated geometries for 7-norbornene, its cation, and anion. The values for norbornene and the second value for the ions are from Santry[33]; others, from Dewar[34]

was about the same as in norbornene. One might have expected an increase in the magnitude of θ, reflecting a decrease in orbital interaction due to bishomoantiaromaticity. Decreased orbital interaction is suggested, at least in Dewar's calculations, by the magnitude of angle ϕ for the 7-anion. When angle ϕ is > 180, the proton is syn to the π-bond, and the lone pair of electrons on C_7 are anti. Obviously, the conformation with the lone pair syn to the π bond is destabilized, which Dewar suggested was due to bishomoantiaromatic interaction.

At the outset of this investigation, experimental data concerning bishomoantiaromatic anions was lacking. Since that time, however, some papers have appeared which relate to our work. In 1970, Breslow[35] reported results of competitive H-D exchange in anti-7-cyanonorbornene (XXIII) and 7-cyanonorborane (XIV). The reactivity ratio, k_{XXIII}/k_{XXIV}, was 1.4.



XXIII

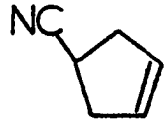


XXIV

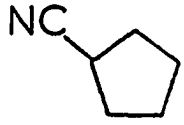
$$\frac{k_{XXIII}}{k_{XXIV}} = 1.4$$

It was predicted that k_{XXIII} should be less than k_{XIV} due to antiaromatic destablilization of the incipient ion in XXIII. Breslow postulated that the observed reactivity ratio was the result of a combination of inductive stabilization (as indicated in the cyclopentene, cyclopentane

reactivity ratio) and bishomoantiaromatic destabilization.



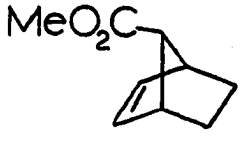
XXV



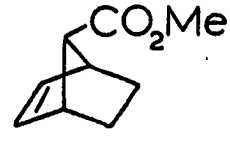
XXVI

$$\frac{k_{XXV}}{k_{XXVI}} = 10$$

Davis and Bigelow[36] contradicted Breslow's explanation of the reactivity ratio on the basis of their results. Relative rates of base catalyzed exchange and isomerization were obtained for syn and anti-7-carbomethoxy norbornene, XXVII and XXVIII, respectively. The reactivity ratio, k_{XVIII}/k_{XXVII}, is again 1.4, even though there are equivalent inductive effects in XXVII and XXVIII. (Breslow's explanation requires differential inductive effects)



XXVII



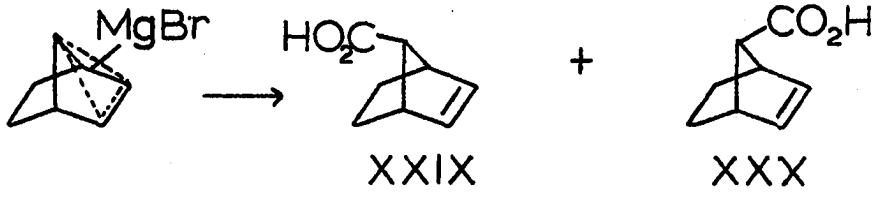
XXVIII

$$\frac{k_{XXVIII}}{k_{XXVII}} = 1.4$$

The authors suggested the slightly greater rate observed for XXVIII was due to relief of B-strain via a syn/anti isomerization. B-strain is the mutual repulsion of crowded atoms or groups of atoms. In this case, steric repulsion between the carbomethoxyl and the exo-protons accounts for the strain. Distortion of bond angles is called I-strain, but is effectively the same for both XXVII and XXVIII. Other possible explanations consistent with the observed results were neglected in both papers.

For example, the slightly greater rate for XXVIII may only reflect the ease of approach of base (approach of base is sterically hindered by the exo protons of XXVII) or, it might indicate the relative stabilities of the anion intermediate due to differential solvation (solvation is more effective for less hindered anions).

Examination of the literature for reactions which might involve a bishomoantiaromatic intermediate or transition state was fruitful. Carbonation of the Grignard reagent of syn-7-bromonorbornene yielded a 2 to 1 mixture of anti XXIX and syn XXX carboxylic acids respectively.[37] Assuming that carbonation occurs with retention of configuration and at a rate greater than syn-anti interconversion, then the product ratio reflects the destabilizing effects of bishomoantiaromaticity. There is ample evidence to support the assumption that carbonation occurs with retention.[37a] Further, temperature dependent proton nmr indicate slow inversion of Grignard reagents at room temperature.[37b] A reasonable overall picture for the reaction is as follows: the initial syn-7-Grignard isomerizes to an equilibrium mixture of syn and anti forms. Carbonation yields a 2 to 1 mixture of carboxylic acids. Each acid is formed sterospecifically from the anion of the same configuration. Hence, the anion with the lone pair anti to the π bond is more stable than the syn anion. This at least implies destabilization due to bishomoantiaromaticity.



XXIX XXX

The Curtin-Hammett principle[38] states that for reactions in which the activation energy for the product forming step is much greater that the activation energy for isomer interconversion ($\Delta G_p^{\ddagger} >> \Delta G_i^{\ddagger}$), the product distribution reflects only the transition state energies of the product forming reaction (represented schematically in Figure 3).

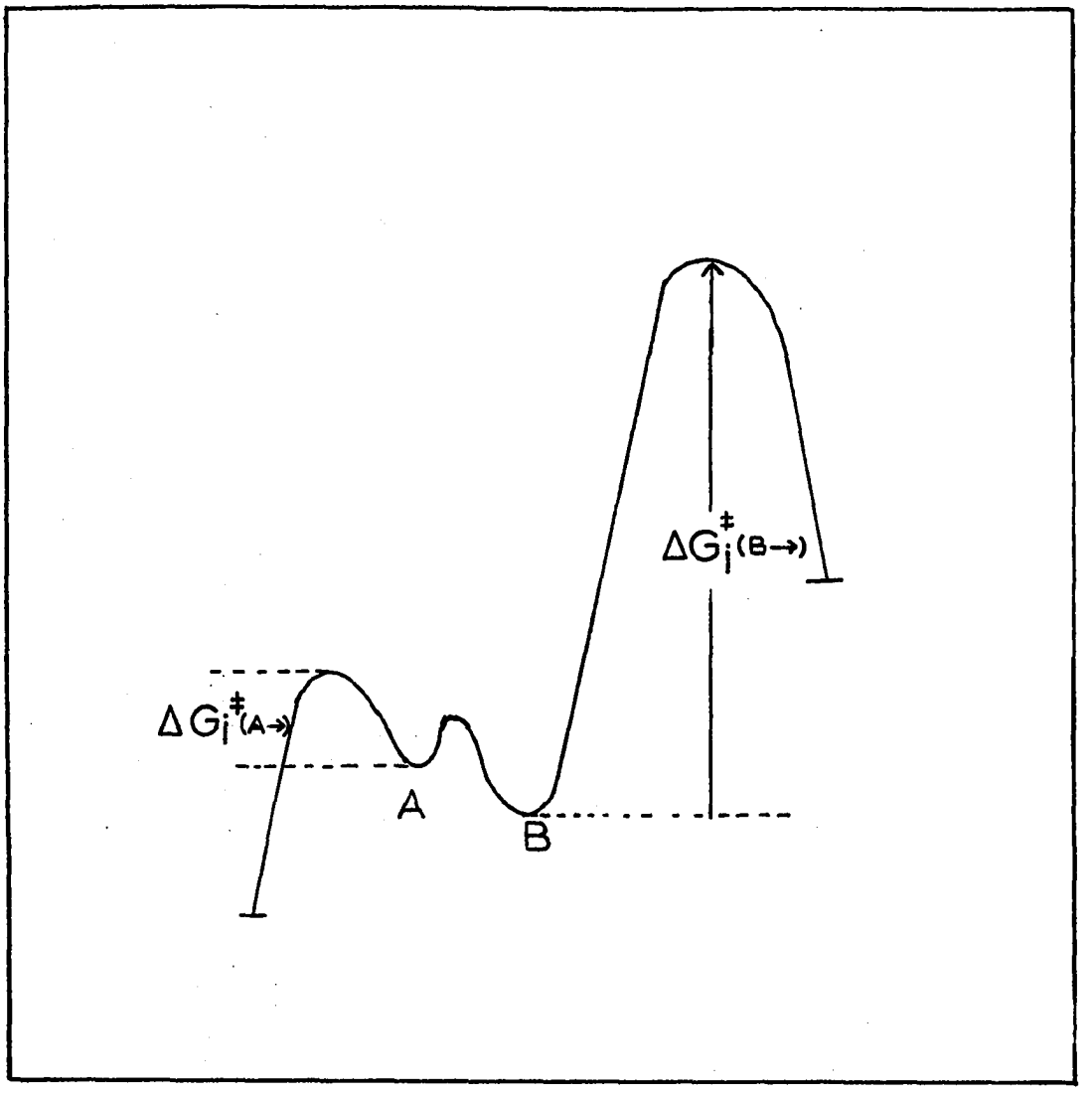
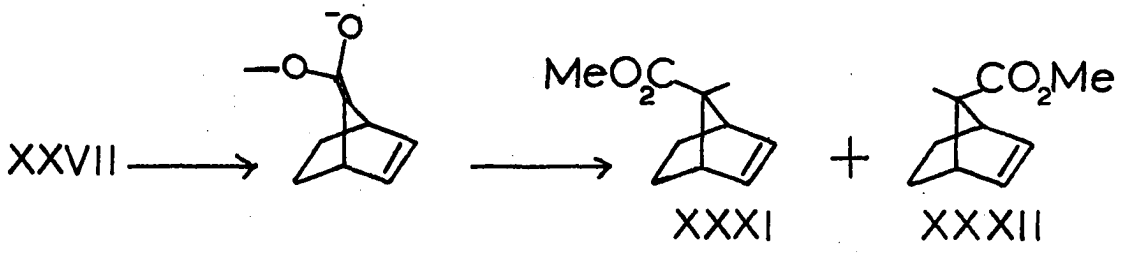
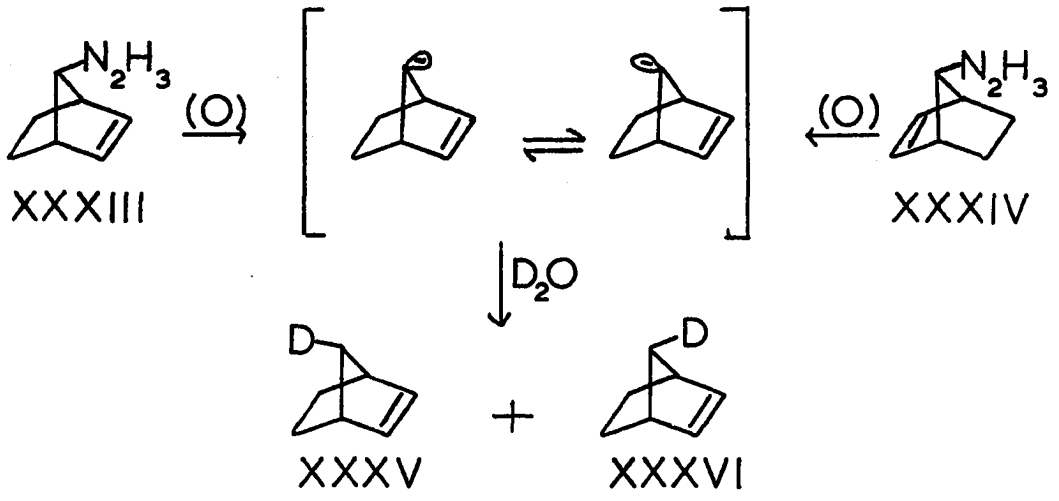


Figure 3. Schematic Representation of Curtin-Hammett Principle.

Although most of the intermediate is the more stable B, the product will contain a majority of molecules from the reaction of isomer A, with smaller activation energy for product formation. The limiting case of this type of kinetic control is indicated when one treats XXVIII with trityl sodium, then CH_3I.[39] The product is an 8:1 mixture of XXXI and XXXII. Here, use of trityl sodium traps the intermediate as its enolate; hence $\Delta G^{\circ}=0$. When both products arise from the same intermediate, the product distribution reflects only the energetics of the product-forming reaction. Steric hindrance to the approach of the electrophile on the anti face (repulsion by exo hydrogens) can best account for the observed product distribution.



The best results yet presented on the destabilizing effects of bishomoantiaromaticity were published in 1972 by Stille and Sannes.[40] They generated the 7-norbornenyl anion by basic oxidative cleavage of syn-and anti-7-norbornenyl hydrazines, XXXIII and XXXIV, respectively. Treatment of either with potassium periodate and potassium t-butoxide in D_2O or deuterated t-butyl alcohol resulted in identical mixtures of 93% anti-7-deuterio and 7% syn-7-deuterionorbornene, XXXV and XXXVI, respectively.

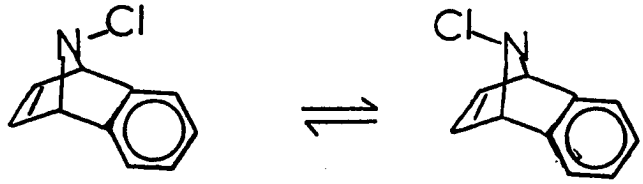


The author suggested that the product ratio, which is unchanged regardless of starting material or solvent, is consistent with slow, irreversible formation of the anions, followed by their rapid equilibration and subsequent capture by deuterium. The implied predominance of the anti- carbanion reflects the destabilizing effects of bishomoantiaromaticity in the syn- carbanion. One point not mentioned by the authors, however, is the possibility that the product distribution does not reflect the anion distribution due to an unobserved secondary reaction. An example might be that the syn- anion had a secondary reaction, such as nucleophilic attack on the double bond followed by further decomposition, which was not possible for the anti- anion. If this occurred, the product distribution would be incorrectly weighted towards XXXVI. This is certainly possible in view of the 50% unidentified products.

Examining the thermodynamic stability of the intermediates, without the intervention of product forming reactions. secondary reactions, etc., is difficult. The problem is greatly simplified, however, by use of a heterocyclic model. Direct observation of the thermodynamic equilibrium between two invertomers of an amine is possible through the use of temperature dependent proton nmr. Kinetic data is also available by this technique, and in fact, this was one of the earliest uses of variable temperature nmr spectroscopy. Activation energies for nitrogen inversion in aziridines were obtained as early as 1960.[41] In amines where $\Delta G^{\circ}=0$ (equal populations of invertomers) calculation of the activation energy from the proton nmr is relatively simple.[42] For molecules where the states are not equally populated, $\Delta G^{\circ}\neq 0$, calculations of the activation energy is more difficult. Calculation of $\Delta G^{\ddagger}$ requires the solution of the Bloch equations,[43] and this is usually handled by computer generation of trial functions which are matched with experimentally obtained spectra.

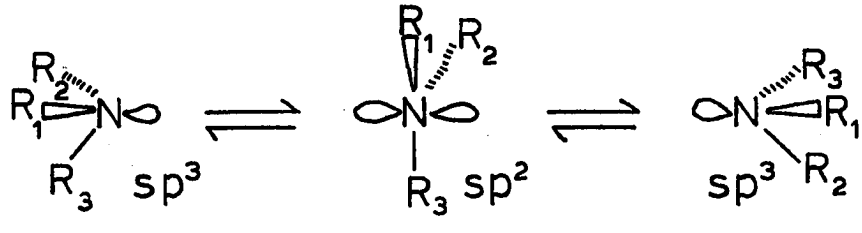
For unequally populated states, determination of ΔG° by nmr spectrometry is simple[44] provided the equilibrium constant is within $0.05 < K < 20$ (if the population of one invertomer is > 98%, observation of the minor component is difficult). The temperature of coalescence

must be in the practically obtainable range of $-150° < T_c < +150°$. Finally, the chemical shift difference of invertomers must be sufficiently unique so that accurate integration of the signals is possible. For example, the equilibration of anti-7-chloro-7-azanorbornadiene (XXXVII) at room temperature[45] yields a mixture of 60% syn-7-chloror-7-azabenzonorbornadiene (XXXVIII) and 40% XXXVII.



XXXVII XXXVIII

ΔG° is obtained directly from electronic integration of the proton nmr spectra. The activation energy for this inversion is $\Delta G^{\ddagger}$=16 kcal/mole.[45] This represents a much higher barrier than for simple aliphatic amines which average 6-8 kcal/mole.[46] The reason is twofold: a) electron donating groups like Cl- tend to destabilize and sp^2 transition state which is a necessary intermediate in inversion,[47]



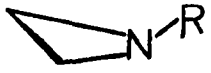
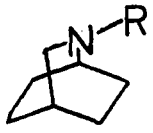
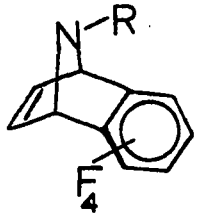
and b) I-strain likewise destabilizes the sp^2 transition state.[48] Conversely, electron withdrawing groups decrease $\Delta G^{\ddagger}$ by stabilizing the sp^2 transition state.

The effect of electron withdrawing and donating groups and I-strain is apparent in the following comparisons of $\Delta G^{\ddagger}$ in Table 1. By comparison of the structural details of XVI, XVII, XVIII, and XIX, with the $\Delta G^{\ddagger}$, β values listed in Table 1, we can make at least crude approximations as to expected activation energies, and hence coalesence temperatures.[51] For example, XVI and XVII are structurally similar to the last entry in the table (#9). Assuming models XVI and XVII are slightly less strained than entry #9, $\Delta G^{\ddagger}$ should be slightly lower and coalesence temperatures should be slightly lower. Therefore, we know for XVI and SVII that the upper limit fot T_c is ca. -50°. Likewise, XVIII and XIX are slightly more strained than entry #7, therefore, $\Delta G^{\ddagger}$ should be slightly greater than 8.4 kcal/mol and T_c should be slightly > -98°. To obtain the equilibrium constant (and hence $\Delta G°$) in XVI, XVI, XVII, and XIX, it is necessary to cool the sample down until the temperature is below coalesence. Then, by integration of the N-methyl nmr absorption signal, (or any signal which allows an accurate integration) we can determine the relative populations of the two invertomers. In order to assign the appropriate invertertomers to their populations, we need only compare chemical shifts with those of carbocyclic analogs. From Table II it is clear that in every case, the methyl group of the syn isomer absorbs at a higher field than the anti isomer. This might be expected from the fact that the syn methyl groups are in a shielding region (above the plane) of the double bond or benzene ring.

The following is a brief summary of our expectations for the temperature dependant nmr of XVI thru XIX.

Somewhere between 0 and -50 we expect to see the N-methyl singlet of XVII and XVIII separate into two signals.

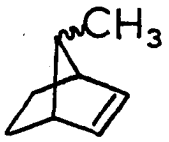
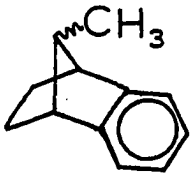
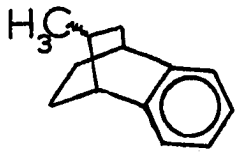
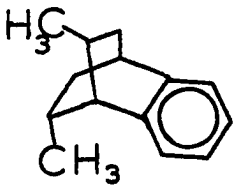
Table 1

	-R	$\Delta G^{\ddagger}$	Reference
	1) Me	22.4	49
	2) Ts	12.4	52
	3) Me	10.6	50
	4) Cl	13.8	50
	5) Tosyl	6.2	50
	6) Cl	10.6	53
	7) Me	8.4	53
	8) Cl	23.5	45
	9) Me	14.0	54

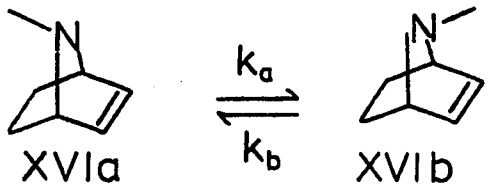
Activation energy for nitrogen inversion for serval amines.

Table II

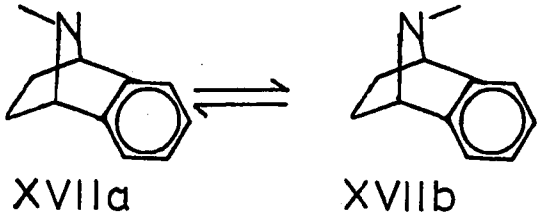
Chemical Shift in PPM From TMS

	Syn	Anti	Reference
	0.70	0.79	55
	0.67	0.91	57
	0.46	1.0	56
	0.47	1.04	56

Chemical shift of <u>syn</u> and <u>anti</u> methyl groups in a few bicyclic alkenes.

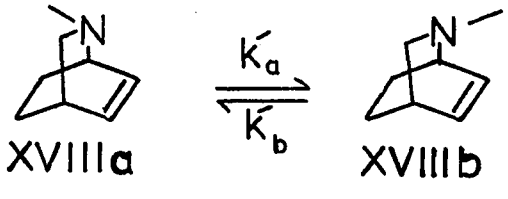


$$K = \frac{k_b}{k_a} > 1$$

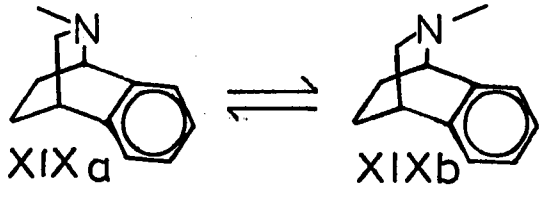


Due to bishomoantiaromatic destabilization in XVIa and XVIIa, we predict K > 1, and hence, invertomers XVIb and XVIIb will predominate. This will be represented by the major component (b) being upfield of the minor, (a).

In XVIII and XIX due to decreased I-strain, we expect coalesence somewhere between -50° and -100°. For the nonsymmetric interaction of the nitrogen lone pair with the π orbitals, we predict stabilization due to favorable homoallylic conjugation. For XVIII and XIX, we suggest that the more stable invertomer is (a), hence $K' < 1$. In these cases, the nmr should indicate the major component downfield of the minor component.



$$K' = \frac{K'_b}{K'_a} < 1$$



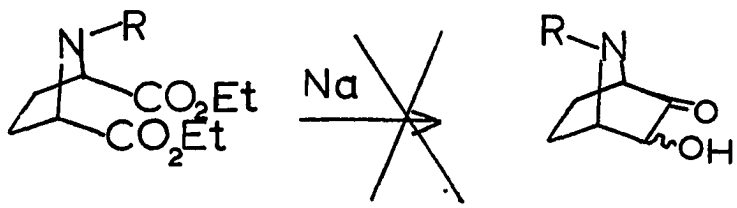
Before discussing the results of the dynamic nmr studies, I will discuss the synthesis of XVI-XIX. Of the four bicyclic amines, only N-methyl-5-azabicyclo(2.2.2)oct-2-ene, has previously been prepared.[58] The discussion will begin with the synthesis of the 7-azabicyclo(2.2.1) hept-2-ene system.

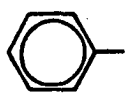
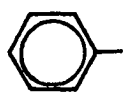
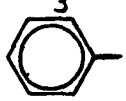
When we began this work, the only known method of preparing the 7-azabicyclo(2.2.1)heptenyl skeleton employed Diels-Alder reactions between substitutued pyrroles and acetylene derivatives.[59-63] The yields were generally poor and could only be used to prepare highly substituted derivatives. A synthesis of 7-azabicyclo(2.2.1)heptane has recently been reported.[64] However, attempts to convert it to 7-azabicyclo(2.2.1)heptene via elimination of HCl from the exo-2-chloro derivative were unsuccessful.[64] The only bonafide synthesis of an N-substituted 7-azabicyclo(2.2.1)heptene has been described by Hoesch and Dreiding.[65] N-phthalimido-7-azabicyclo-(2.2.1)heptene was prepared in 7% yield by isomerizing N-phthalimido-7-azabicyclo(4.1.0)hept-2-ene. But again, attempted conversion to the parent amine was unsuccessful. Other methods, such as cyclizing various cyclohexylamine derivatives,[66,67] and cycloaddition of azalactones[68-70] have produced only substituted 7-azabicyclo(2.2.1)heptanes.

Our first attempt toward the synthesis of XVI involved ring closure of N-methyl-cis-2,5-dicarboethoxy pyrrolidine employing a modified acyloin condensation.[77] This reaction has been shown to be useful for the synthesis of both small[71,72] and large rings.[73-75] The mechanism of

the cyclization is presumed to be an initial bimolecular reduction of the diester to a semidione, followed by ring closure and futher reduction. Numerous attempts at effecting this condensation on N-alkyl cis-2,5-dicarboethoxy pyrrolidine met with failure, save one isolated run which could not be reproduced.[76]

The following is but a partial listing of the various conditions we employed.

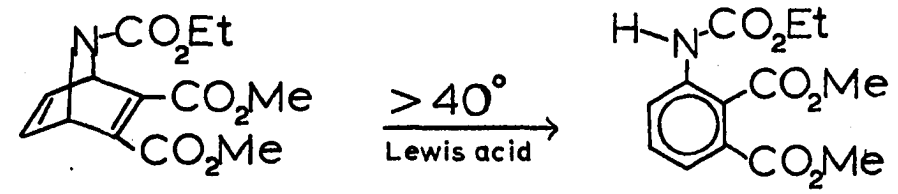


Electron Donor	Solvent	Temperature
Na		reflux
Na		reflux
Na		25, 50, 80°
Na Naphthalide	THF	RT, 0°
Na	NH_3	-30°
Na/K		0, 25°, 50°, 80°, 110°

Most of the reaction conditions were duplicated with addition of chlorotrimethylsilane, which has been shown to be useful for preparing strained rings[77] via acyloin formation.

The failure of the acyloin condensation forced us to reconsider the Diels-Alder reaction for the preparation of XVI. Initially we chose the method of Bansal et al.[61] to prepare N-carboethoxy-2,3-dicarbomethoxy,

7-azabicyclo(2.2.1)hepta-2,5-diene, XXXIX. Although the product was obtained in about 80% yield, two factors mitigated against its use synthetically: to obtain even gram quantities of pure product required large scale column chromatography Secondly, traces of Lewis acids caused isomerization of XXXIX to the aminophthalate ester.[61]



XXXIX

Similar rearrangements have been observed for substituted 7-oxabicyclo (2.2.1)heptadienes[78] and 7-thiabicyclo(2.2.1)heptadienes.[79]

For the reasons cited, we decided to seek an alternant starting material. The Diels-Alder adduct of N-benzyl pyrrole and acetylene-dicarboxylic acid is obtained in only 18% yield.[80] However, its ease of isolation and thermal stability outweigh the low yield. N-benzyl 7-azabicyclo(2.2.1)hepta-2,5-diene-2,3-dicarboxylic acid (XL) is easily isolated from the crude reaction mixture by repeated washing with hot acetone. Zwitterionic XL is insoluble in acetone and can be recrystallized from boiling H_2O with only slight decomposition. Beginning with XL, figure 4 outlines the reaction schemes employed in the synthesis of 7-azabicyclo(2.2.1)heptene and N-substituted derivatives.

Hydrogenation-hydrogenolysis of XL is effected by 3 moles H_2 over 10% Pd/c. The reduction, conducted in aqueous solution, normally produced XLII which wasn't isolated. The aqueous solution was treated

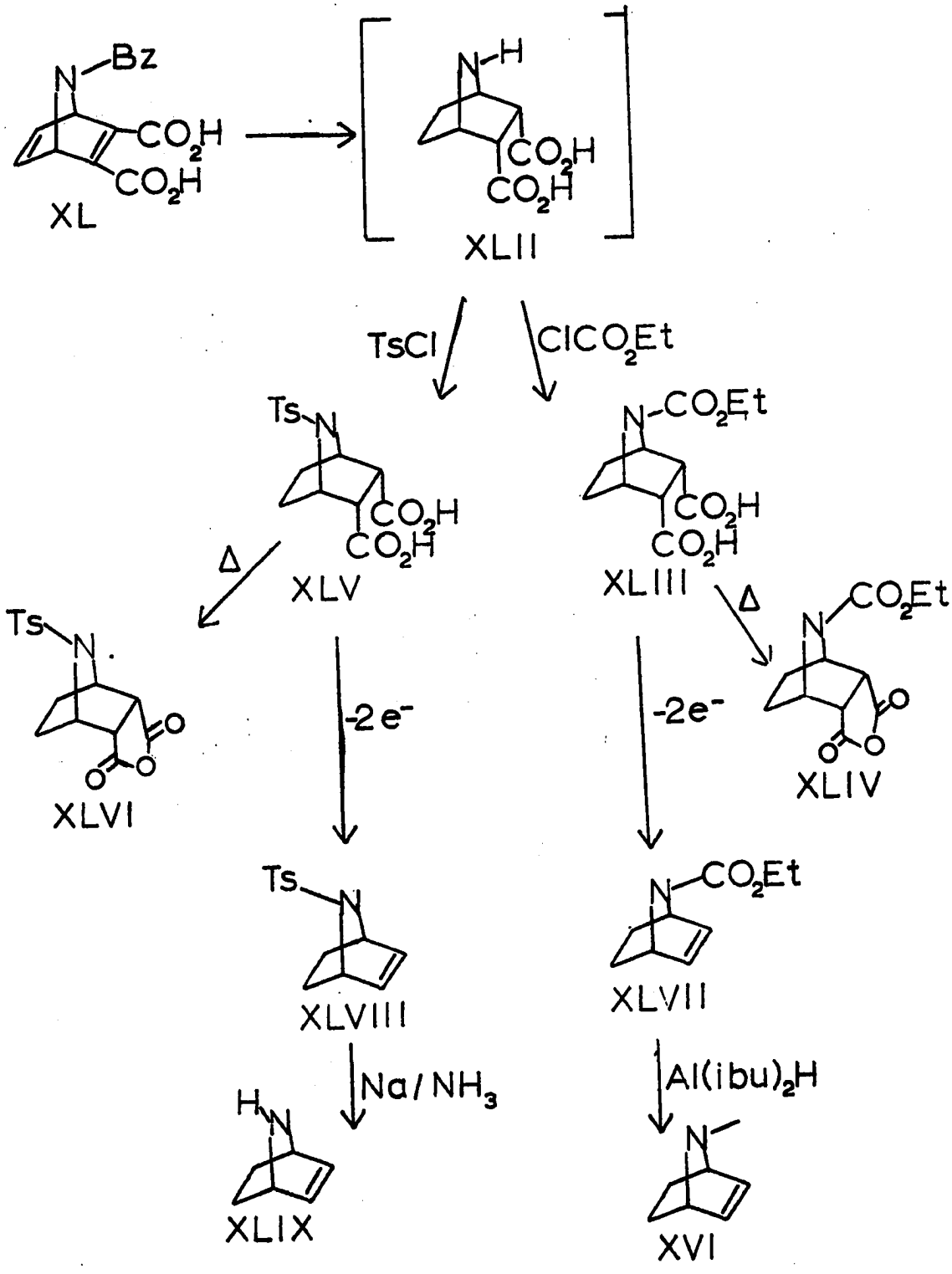
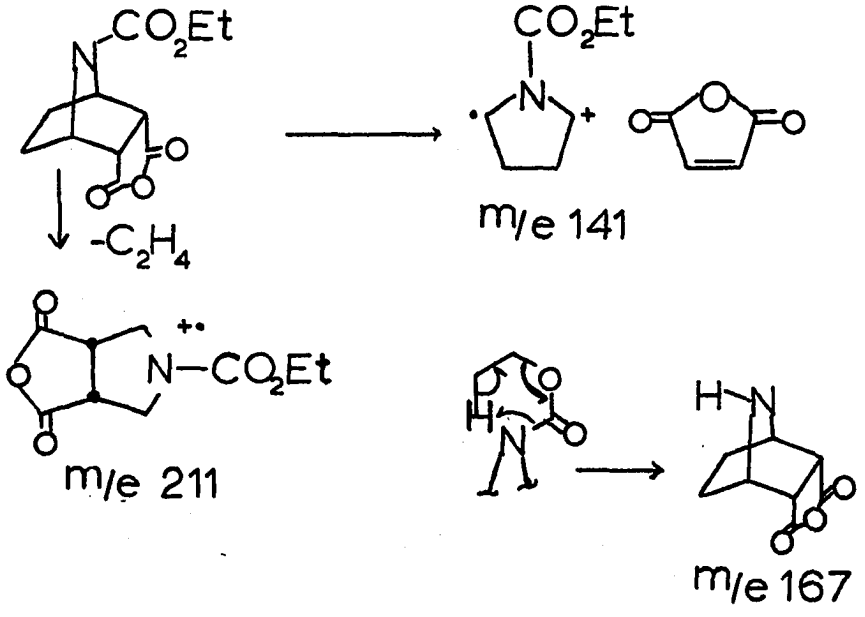


Figure 4. Reaction scheme for the synthesis of several 7-azanorbornenes

with ethyl chloroformate, to yield N-carboethoxy-7-azabicyclo(2.2.1) heptane-2,3-endo,endo-dicarboxylic acid, XLIII. Occasionally, catalyst poisoning stopped the reaction after uptake of only one mole hydrogen, yielding XLI.[81] Compound XLIII is an intractable syrup, but vacuum sublimation converts it to the crystalline cyclic anhydride, XLIV. The nmr and mass spectra are presented in figures 5 and 6.

Assignment of the endo stereochemistry to XLIV follows from the preferred mode of addition of H_2 to norbornene.[84-86] The nmr is also consistent with this assignment.[83] If the 2,3-dicarboxylic anhydride group were exo, the 2,3 endo protons would appear as a singlet. The multiplet at ca. δ 3.7 is due to the 2,3 exo protons which are coupled to the 1,4 bridgehead protons at δ 4.70, (complete proton assignments listed in experimental). Characteristic ions in the mass spectra of XLIV included the parent ion, loss of ethylene, loss of maleic anhydride, and a McLafferty rearrangement[82] product.



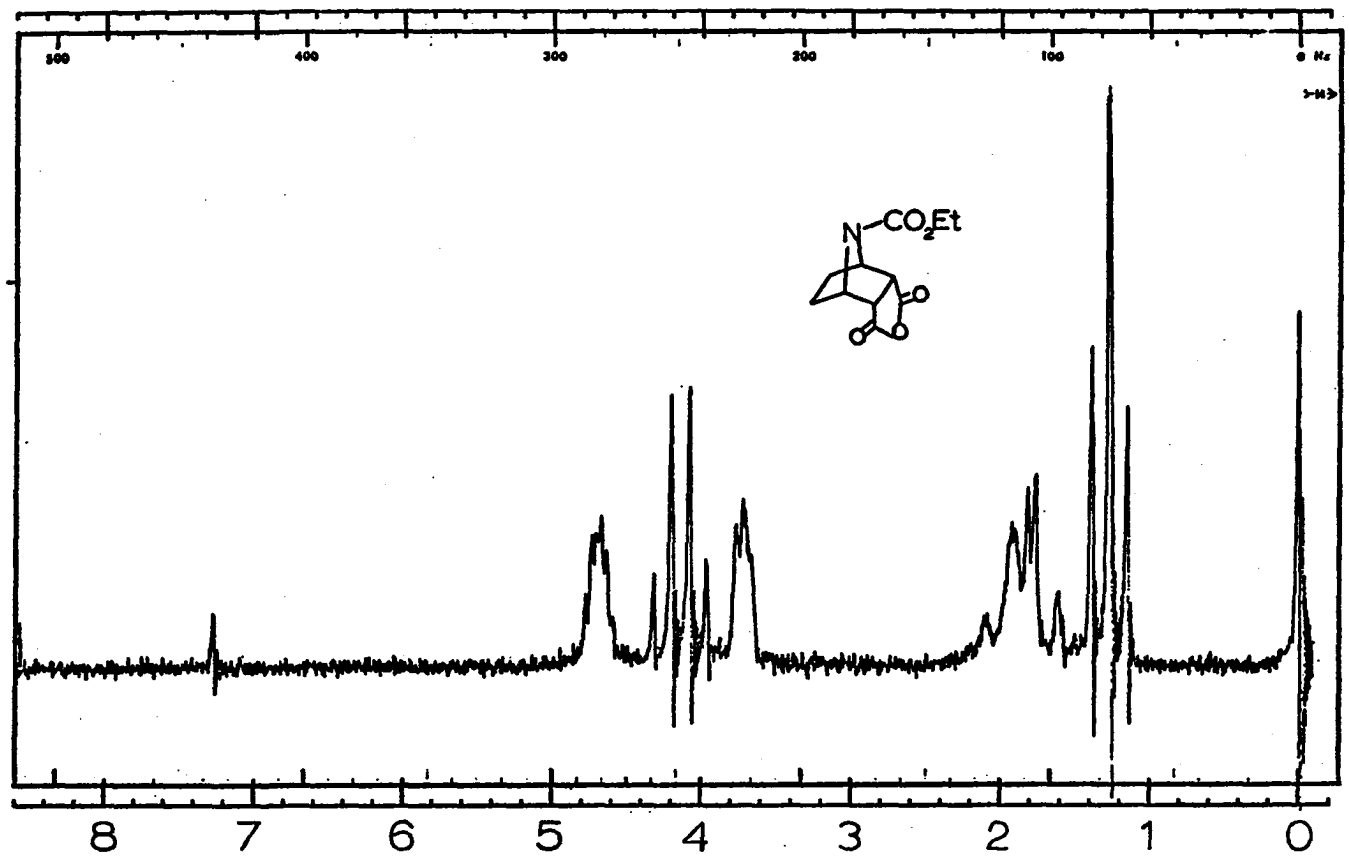


Figure 5. 60 MHz nmr of XLIV, $CDCl_3$ Solution

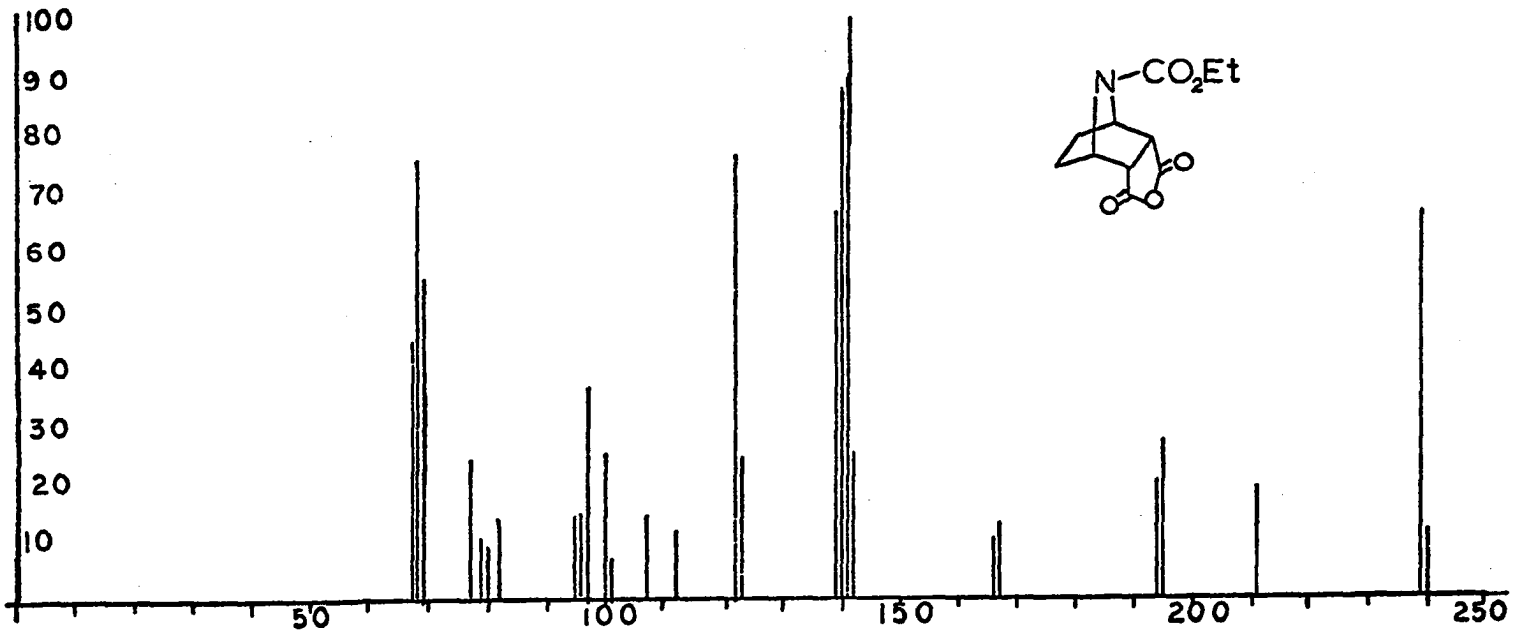
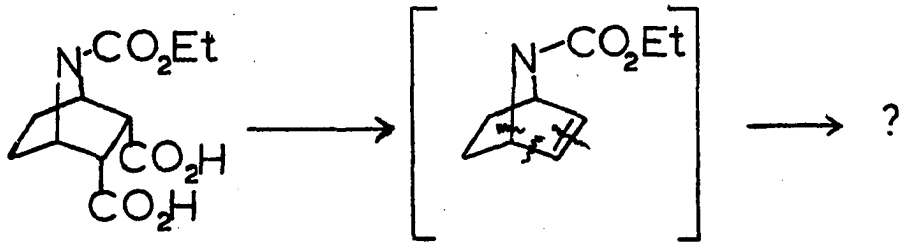


Figure 6. 70 eV mass spectrum of XLIV

A procedure analogous to that used to prepare XLIII was employed for the synthesis of N-Tosyl-7-azabicyclo(2.2.1)heptane-2,3-cis,endo dicarboxylic acid, XLV. The corresponding cyclic anhydride, XLVI could be obtained by vacuum sublimation of XLV at temperatures in excess of 100°. Shown in figures 7 and 8 are the nmr of XLV and the mass spectra of XLVI Respectively.

The next step in the synthetic sequence requires an oxidative bis-decarboxylation to produce the 7-azabicyclo(2.2.1)hept-2-ene skeleton. Lead dioxide was first used to effect bis-decarboxylations of 1,2-dicarboxylic acids. However, the yields were variable and always low.[87,88] Subsequently, Grob[89] found that lead tetraacetate gave consistently better yields. Attempts to effect oxidative bis-decarboxylation of the N-carboethoxy diacid with lead tetraacetate gave variably disappointing results. Varying combinations of pyridine, benzene and dimethyl sulfoxide were employed as solvents.[90] On all occasions only traces of products were obtained, along with products resulting from varying degrees of starting material decomposition.

In those cases where a reaction did occur, the absence of product may be due to further reaction of the strained double bond, either by acetoxylation of the double bond[91] or cleavage of the allylic carbon-nitrogen bond.[92]



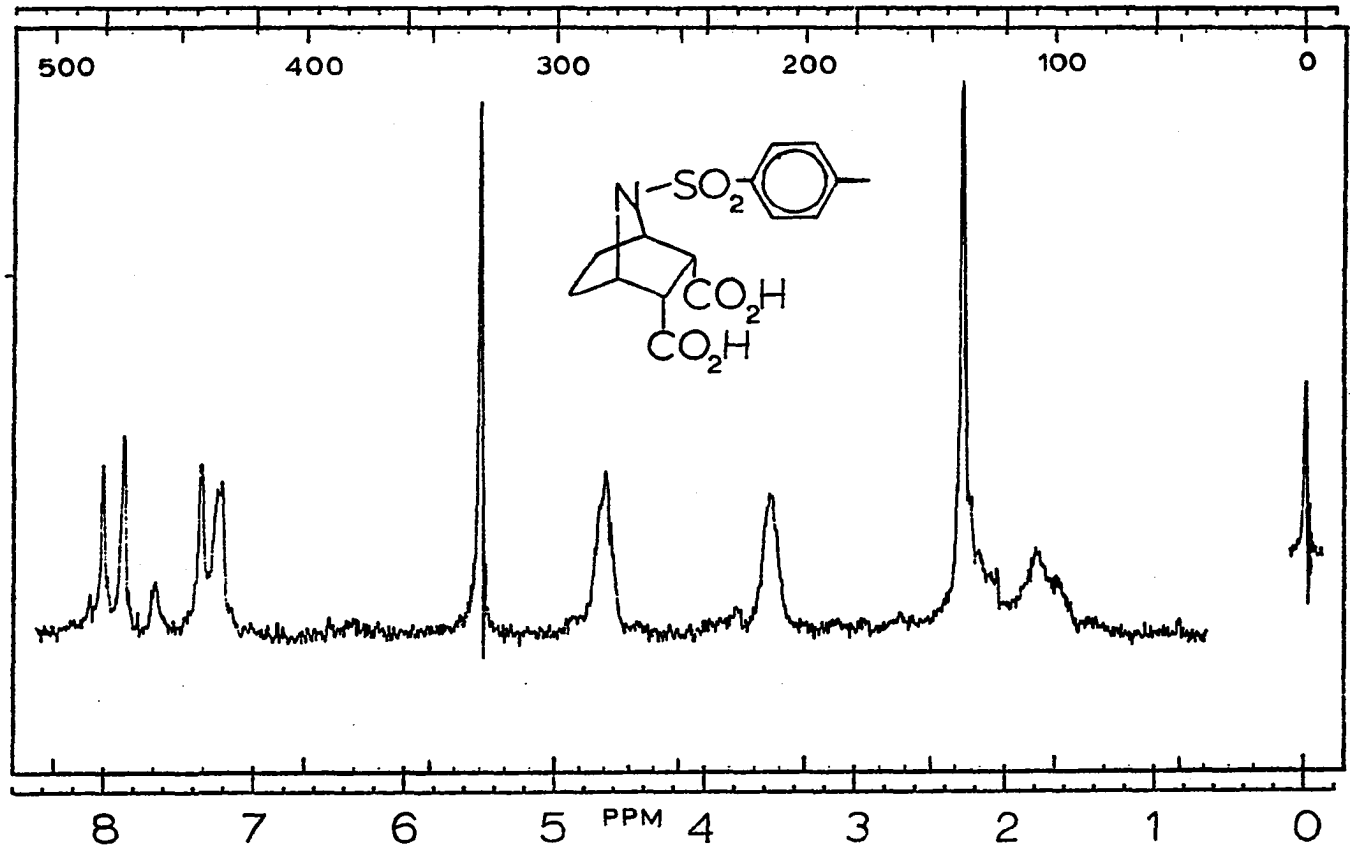


Figure 7. 60 MHz nmr spectrum of XLV, C_5D_5N

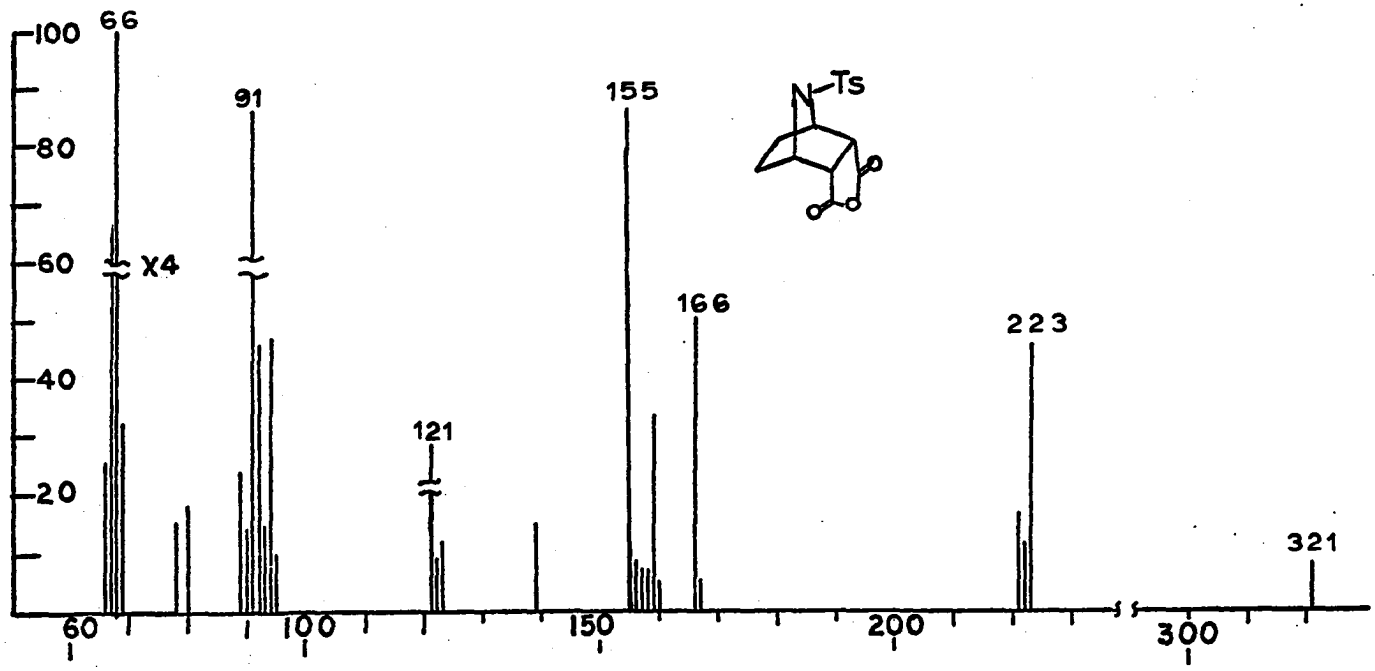
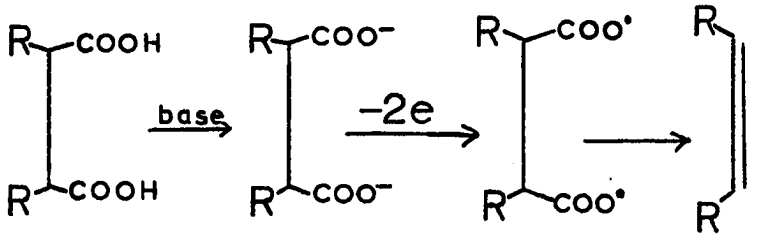


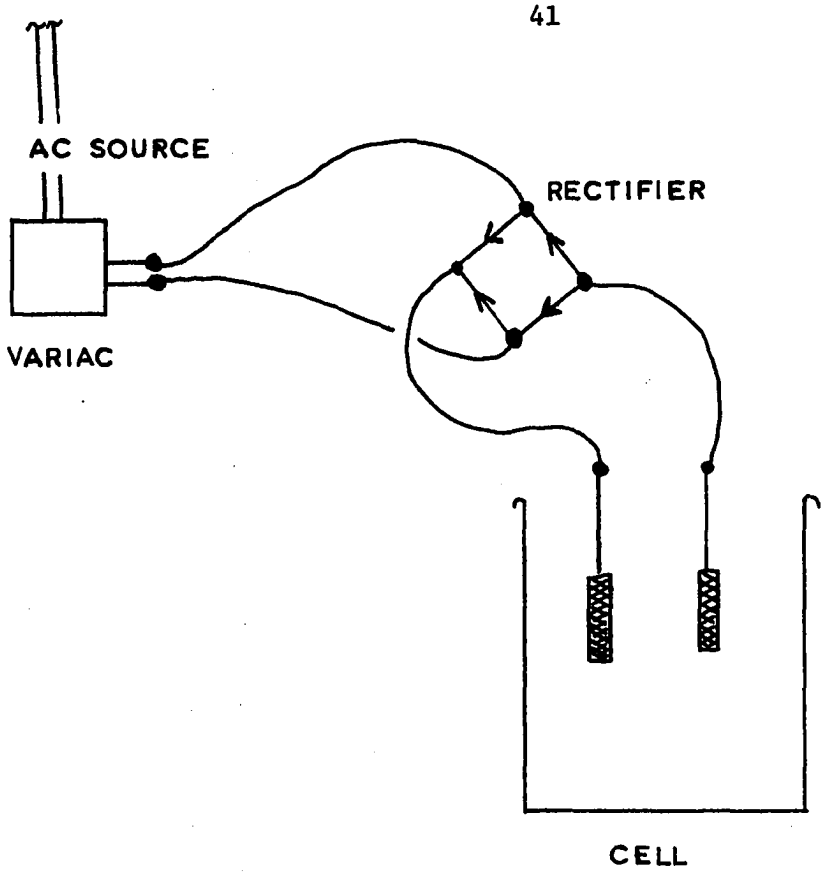
Figure 8. 70 eV mass spectrum of XLVI

Somewhat better results were obtained via electrolytic bis-decarboxylation.[93-95] This is an extension of the Kolbe electrolysis,[96] which is used to convert monocarboxylic acids to hydrocarbon dimers, via a free radical mechanism.



Utilizing very simple electrolysis equipment (vide infra) we obtained about a 30% yield of N-carboethoxy-7-azabicyclo(2.2.1)hept-2-ene, XLVII. Electrolytic decarboxylation of the N-tosyl derivative was not quite so successful, affording at best a 12% yield of N-toluenesulfonyl-7-azabicyclo(2.2.1)heptene, XLVIII.

The electrolysis equipment consists of a variable transformer, full wave bridge rectifier, two platinum wire mesh electrodes and an undivided beaker with a means for external cooling. The advantages of this electrolysis cell are obvious: it is both simple and inexpensive. The major drawback lies in the lack of control of reaction conditions. For example, in an undivided cell, the possibility exists for a reaction at the wrong electrode.[97] A second drawback is the uncontrolled potential.



As the electrolysis proceeds and the reagent is consumed, the current drops and the potential at the working electrode (cathode) becomes increasingly negative. This can cause undesired side reactions.[98] For this reason the electrolysis was run to only ca. 80% completion.

In a typical electrolysis experiment, 10-12 mmoles of the diacid was dissolved in 100 ml 10% aqueous pyridine with one ml triethylamine as coelectrolyte. An initial current of 500 mamps (60 to 80 volts) caused sufficient heating of the solution to require external cooling. By the time the current had dropped below one fifth the initial value, the

reaction was terminated. If the reaction is continued for longer periods or if the initial voltage is much greater than 60 to 80 volts, the yield is decreased. In either case the reason is that the voltage is driven to increasingly negative values where secondary oxidative reactions occur.

For either the N-carboethoxy or N-Tosyl derivatives, the workup consisted of simple solvent extraction followed by column chromatography on neutral alumina. N-Carboethoxy-7-azabicyclo(2.2.1)hept-2-ene can be further purified by gas chromatography, as long as all components (injector, column, detector) are maintained below about 150°. Above this temperature, a retro-Diels-Alder reaction occurs, affording N-carbeothoxypyrrole and ethylene. Further purification of N-toluenesulfonyl-7-azabicyclo(2.2.1)hept-2-ene is easily effected by recrystallization.

The nmr and mass spectra of XLVII and XLVIII are shown in figures 9-12. The nmr of XLVII and XLVIII are characteristic of 7-azabicyclo(2.2.1)heptenes. The complete proton assignments are given in the experimental section but I would like to point out a decoupling experiment (inset, figure 9). Coupling between the 1,4-bridgehead protons and the olefinic protons is clearly indicated by irradiation of the signal at δ 4.41 ($H_{1,4}$). The olefinic proton resonance (δ 6.24) collapses to a singlet, width at half height ca. 1-2 Hz. The mass spectra of both XLII and XLVIII are characteristic, exhibiting a large M-28 peak. This common fragmentation is due to the loss of ethylene, a retro-Diels-Alder reaction.

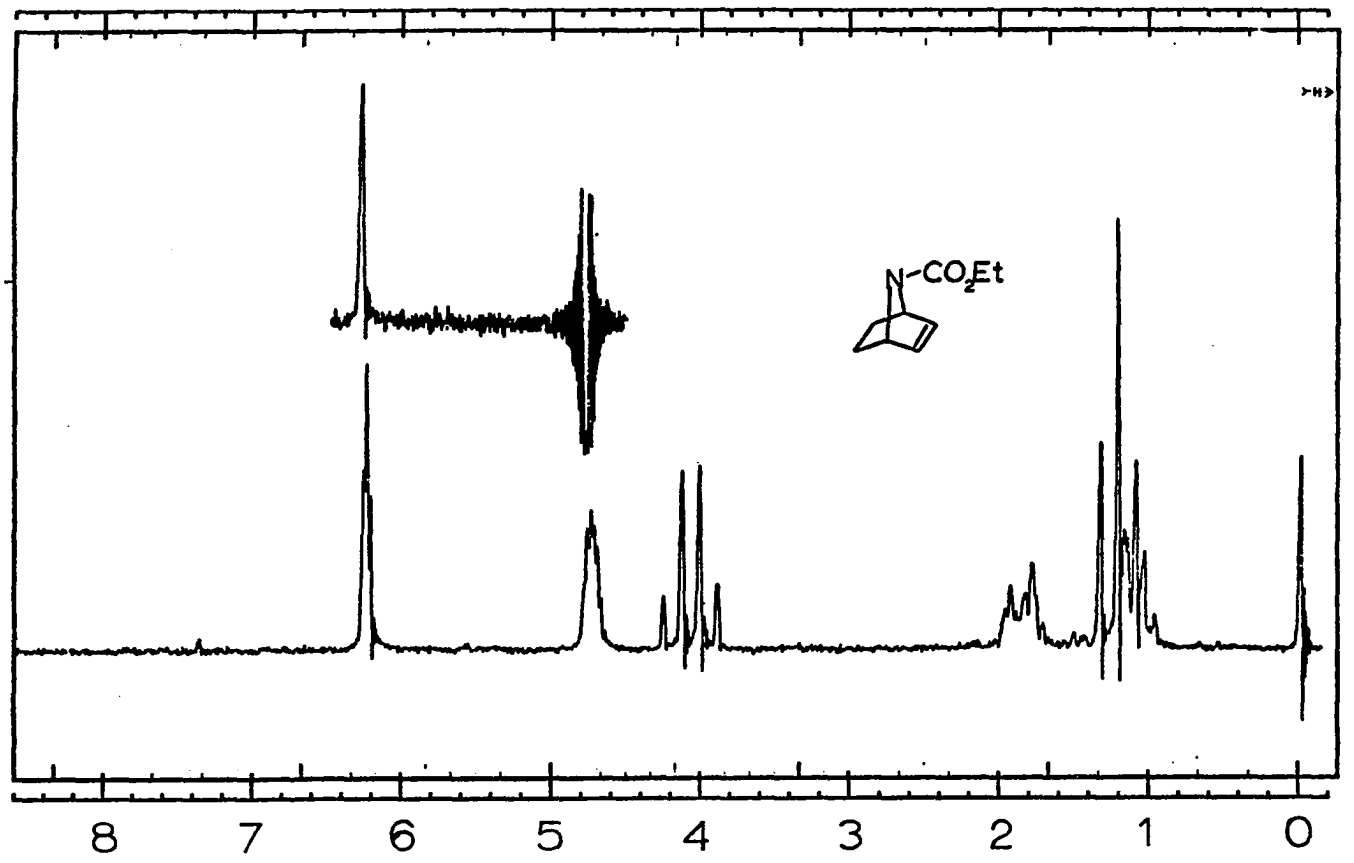


Figure 9. 60 MHz nmr spectrum of XLVII, $CDCl_3$; offset, double irradiation at δ 4.74.

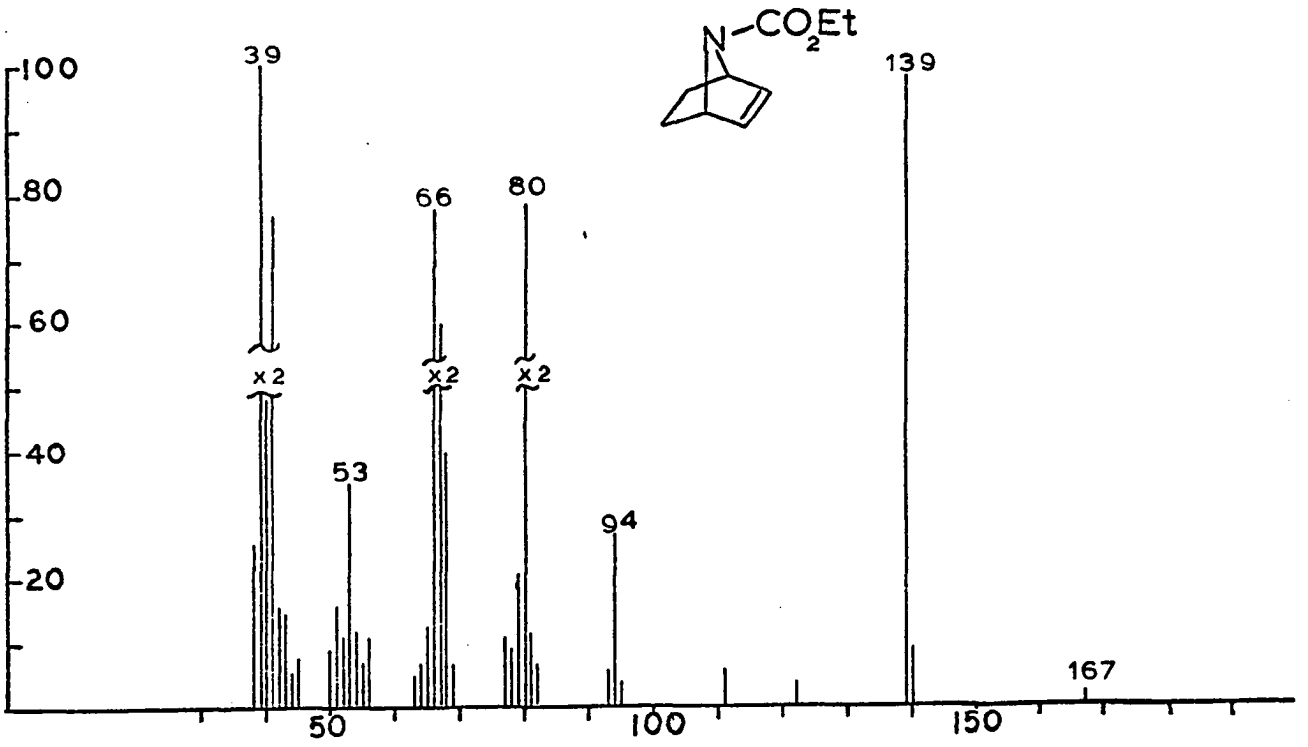


Figure 10. 70 eV mass spectrum of XLVII

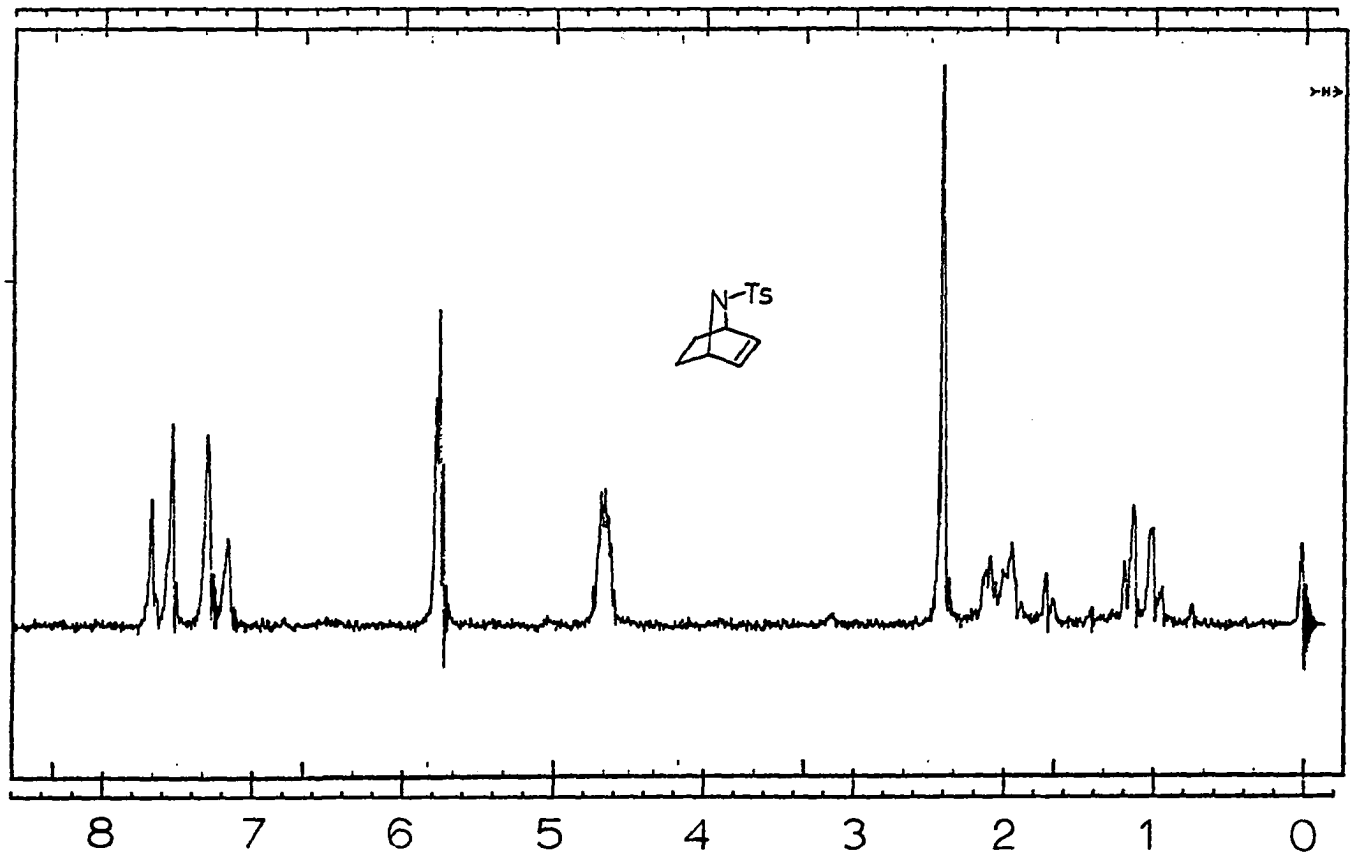


Figure 11. 60 MHz nmr spectrum of XLVIII, $CDCl_3$.

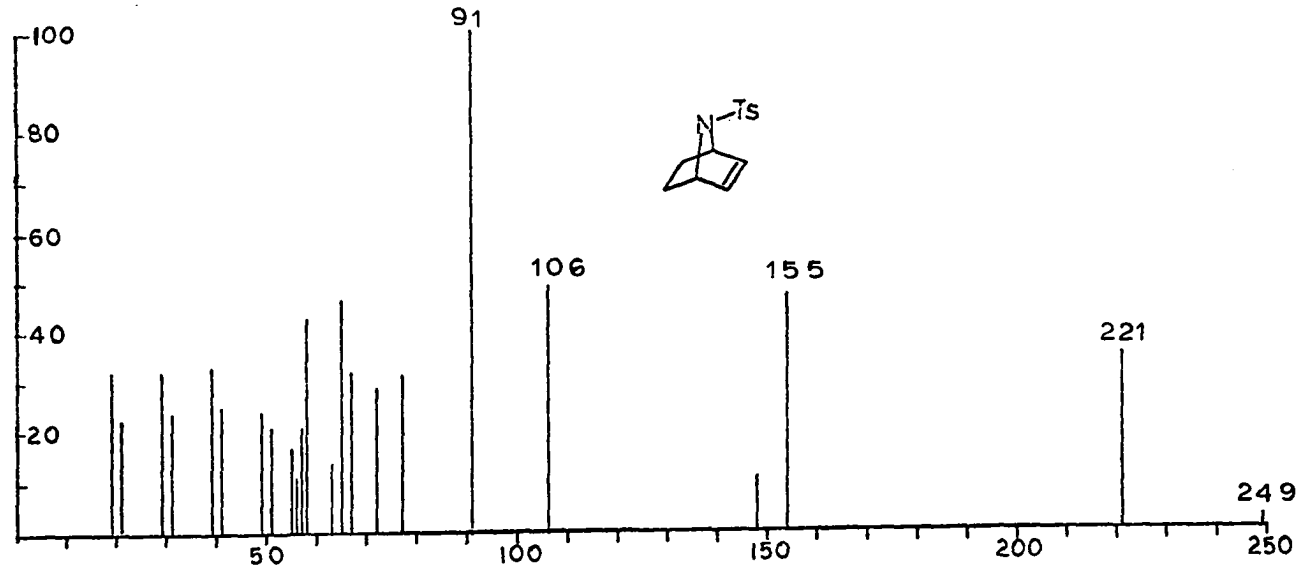
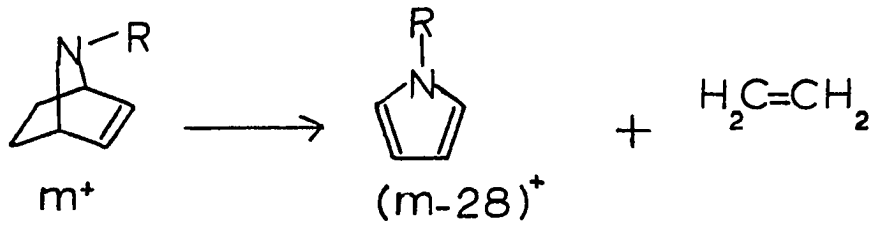
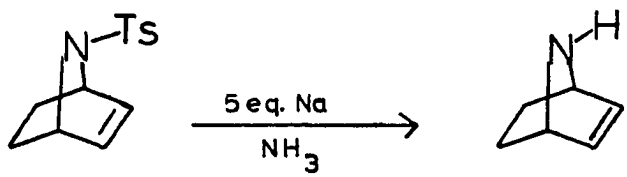


Figure 12. 70 eV mass spectrum of XLVIII.



To complete the synthesis of the unsubstituted parent amine 7-azabicyclo(2.2.1)heptene, XLIX, we initially intended to hydrolyse N-carboethoxy-7-azabicyclo(2.2.1)heptene. The conditions to effect hydrolysis however, lead to a retro-Diels-Alder reaction, as above. Compound XLIX was obtained by reductive cleavage of XLVIII via sodium in liquid ammonia.[99] This method is used for regenerating amino acids in the absence of acidic or basic catalysts.[100,101]



To the best of our knowledge, this represents the first synthesis of this strained secondary amine. The nmr and mass spectra of 7-azabicyclo-(2.2.1)heptene are shown in figures 13 and 14.

The principal compound sought in this work was N-methyl-7-azabicyclo(2.2.1)heptene, XVI. It also proved to be the most difficult to obtain. The synthesis of XVI was frustrated for sometime by our inability to selectively reduce the carboethoxyl group of XLVII to methyl, without simultaneous reduction of the carbon-carbon double

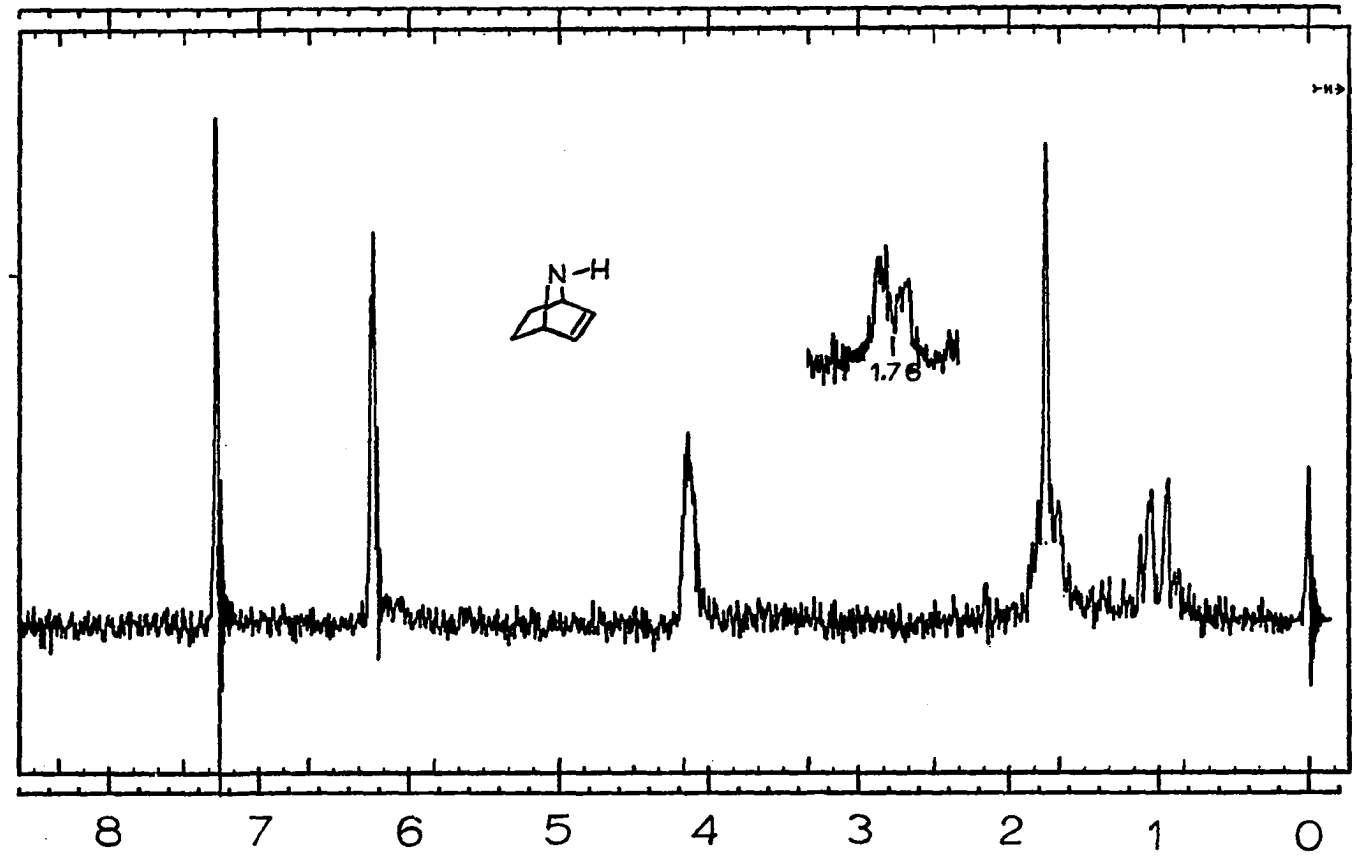


Figure 13. 60 MHz nmr spectrum of XLIX, $CDCl_3$; offset, exo proton region after addition of D_2O.

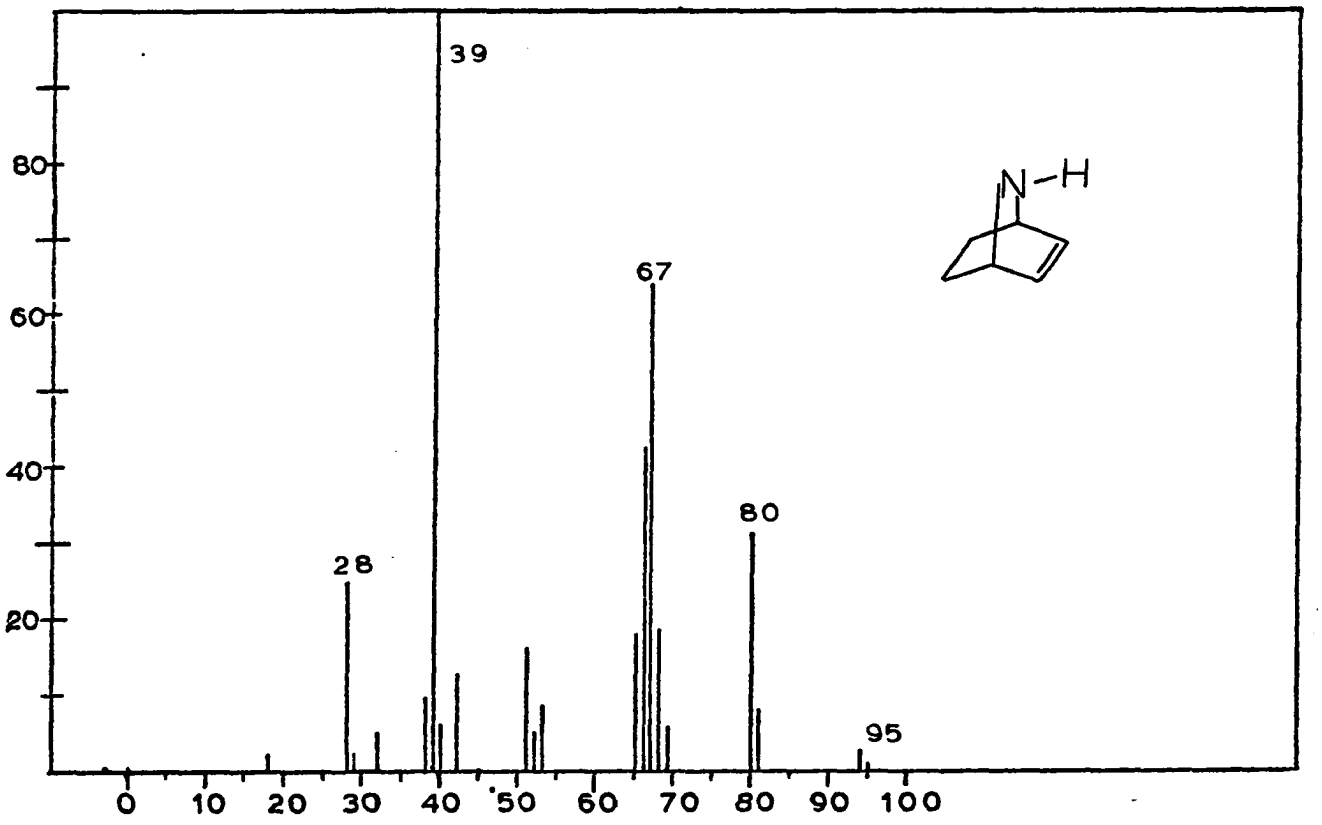
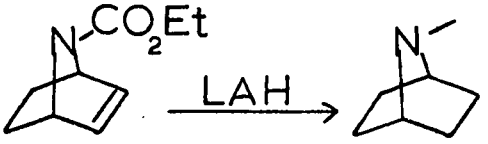
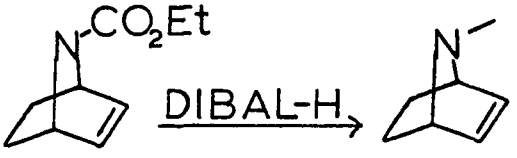


Figure 14. 70 eV mass spectrum of XLIX

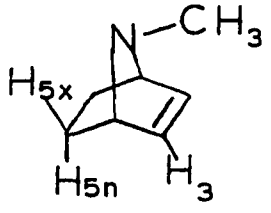
bond.[102,103] It was found that treatment of XLVII with lithium aluminum hydride in ether resulted in complete reduction of the carbon-carbon double bond, even before reduction of the carboethoxyl group was complete!



Running the reaction at various temperatures (35°, RT, 0°, -20°) only altered the overall rate but did not affect the selectivity of the reduction. Similarly, treatment of XLVII with Vitride in ether or benzene at various temperatures again resulted in complete double bond reduction. The problem was finally overcome by employing diisobutyl aluminum hydride[104] in benzene as the reducing agent.



For the synthesis of XVI, 3 to 4 equivalents of diisobutyl aluminum hydride were added to one equivalent of XLVII in benzene. After about 5 hours at room temperature the reaction was worked up with concentrated potassium hydroxide, followed by isolation as the picrate. The free amine is obtained by steam distillation of a mixture of aqueous potassium hydroxide and the picrate salt.



The nmr and mass spectra of XVI are shown in figures 15 and 16.

The nmr of XVI (60 MHz, $CDCl_3$ solution, TMS ref.) is characteristic of the 7-azabicyclo(2.2.1)heptene system: the 5,6 <u>endo</u> protons absorb at highest field as a double doublet at δ 0.96 ($J_{5_n,5_x}$ = 10-11 Hz $J_{5n,6x}$ = 3 to 4 hz). The 5,6 <u>exo</u> proton multiplet appears at δ 1.76. In addition to coupling to the endo protons, the 5,6 <u>exo</u> protons are further coupled to the 1,4 bridgehead protons. The N-methyl singlet is observed at δ 2.04. This resonance is a weighted time-average of the two possible conformatons, (<u>vide infra</u>).

The 1,4 bridgehead proton resonance appears as a multiplet at δ 3.69. The olefinic protons, at δ 5.69 appear as a multiplet (at the ambient probe temperature the olefinic proton signal suffers exchange broadening, hence coupling is not apparent)

The expected feature of the mass spectrum of XVI is the retro-Diels-Alder fragmentation of XVI to ethylene and N-methyl pyrrole, (40% base peak). In fact to observe the molecular ion (even at 10 eV), it was necessary to cool the filament chamber to room temperature. Other important framentations appear at m/e 94 and m/e 80:

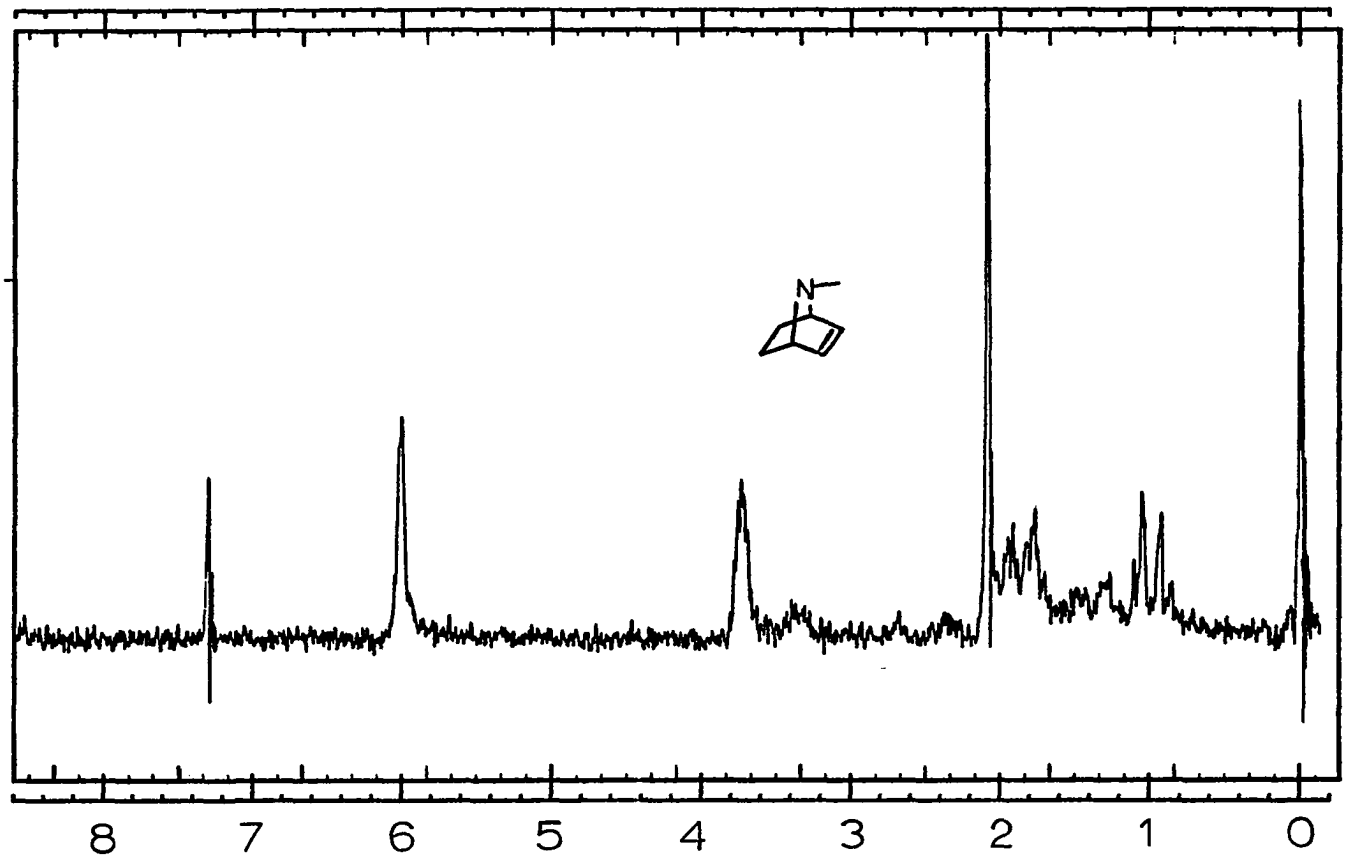


Figure 15. 60 MHz nmr spectrum of XVI, $CDCl_3$.

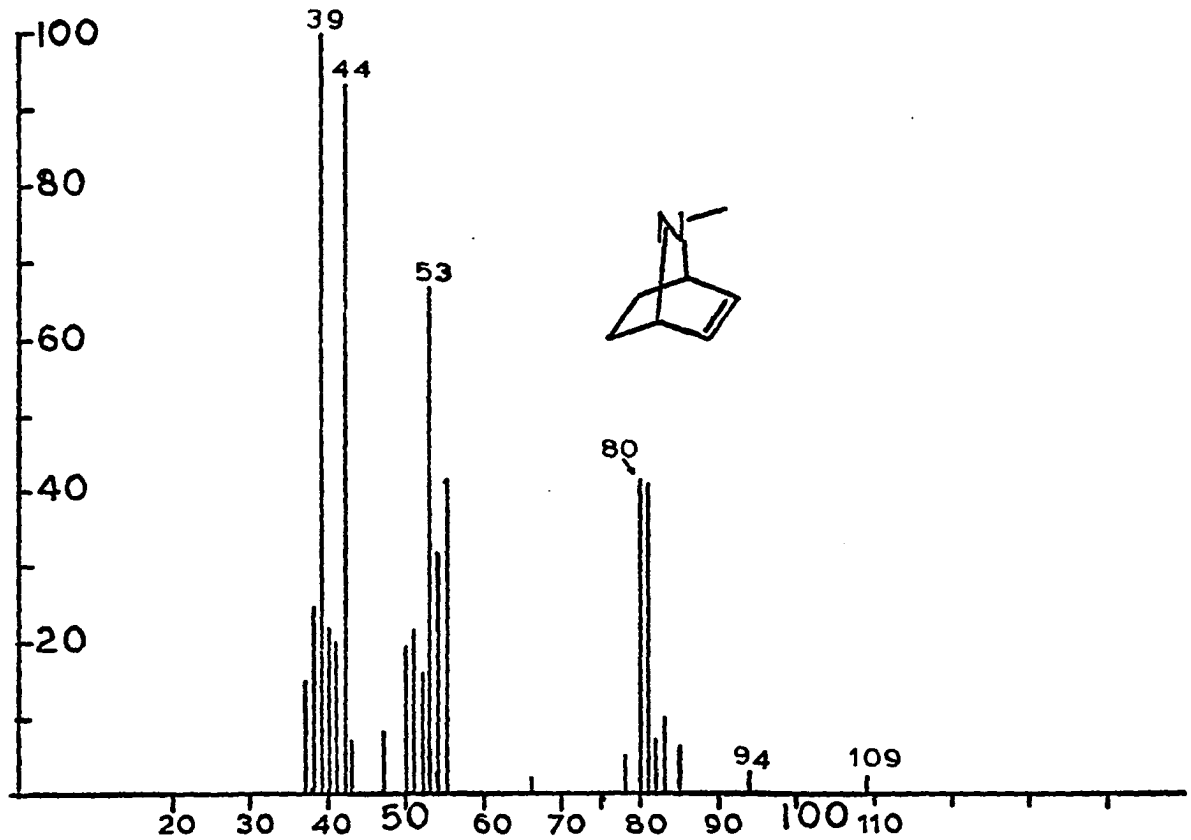
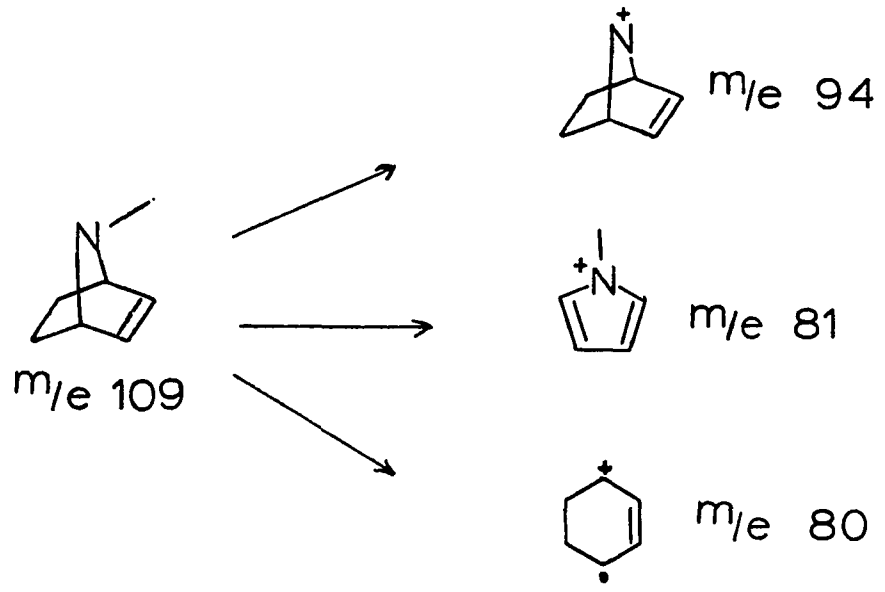
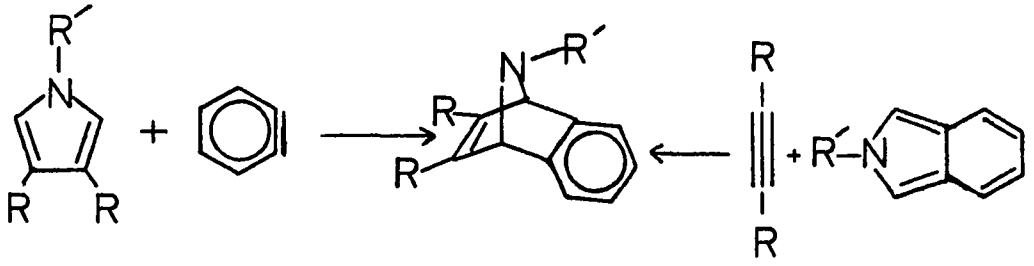


Figure 16. 70 eV mass spectrum of XVI



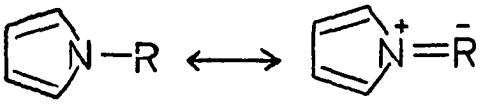
Synthesis of N-Methyl-7-Azabenzobicyclo(2.2.1)heptene (XVII)

Synthesis of XVII, especially when compared to the synthesis of XVI, was extremely simple and straight forward. Two schemes, both of which employ Diels-Alder reactions, have been used to prepare variously substituted naphthalen-1,4-imines[105,106] (Chem. Abstracts nomenclature)[111]



Reaction of N-substituted pyrroles with benzyne (generated in situ) give naphthlen-1,4-imines in yields from ca. 30 to 70%. Generally the yields

are better when R is an electron withdrawing group.[107] This is due to increased contribution from the resonance form on the right, which makes pyrrole less aromatic and hence a better Diels-Alder diene.



The second method for synthesis of naphthalen-1,4-imines involves preparation of isoindole and subsequent reaction with acetylene or ethylene derivatives. For the synthesis of XVII, the more direct approach (the former) was adopted.

N-carboethoxy pyrrole reacts with benzyne, (generated in situ via thermal decomposition of benzene diazonium-2-carboxylate) in refluxing THF to afford N-carboethoxy-7-azabenzobicyclo(2.2.1)heptadiene, L, in 50 to 60% yield. The nmr and mass spectra of L are shown in figures 17 and 18. The proton assignments in the nmr of L are straightforward (listed in experimental section). In the mass spectrum of L the base peak is the molecular ion. The only fragment ion greater than 20% of the base peak corresponds to loss of acetylene, again due to a retro-Diels-Alder reation. Loss of OEt, CO_2Et and N-CO_2Et from the molecular ion are suggested by the presence of major peaks at m/e 170, 142, and 128, respectively.

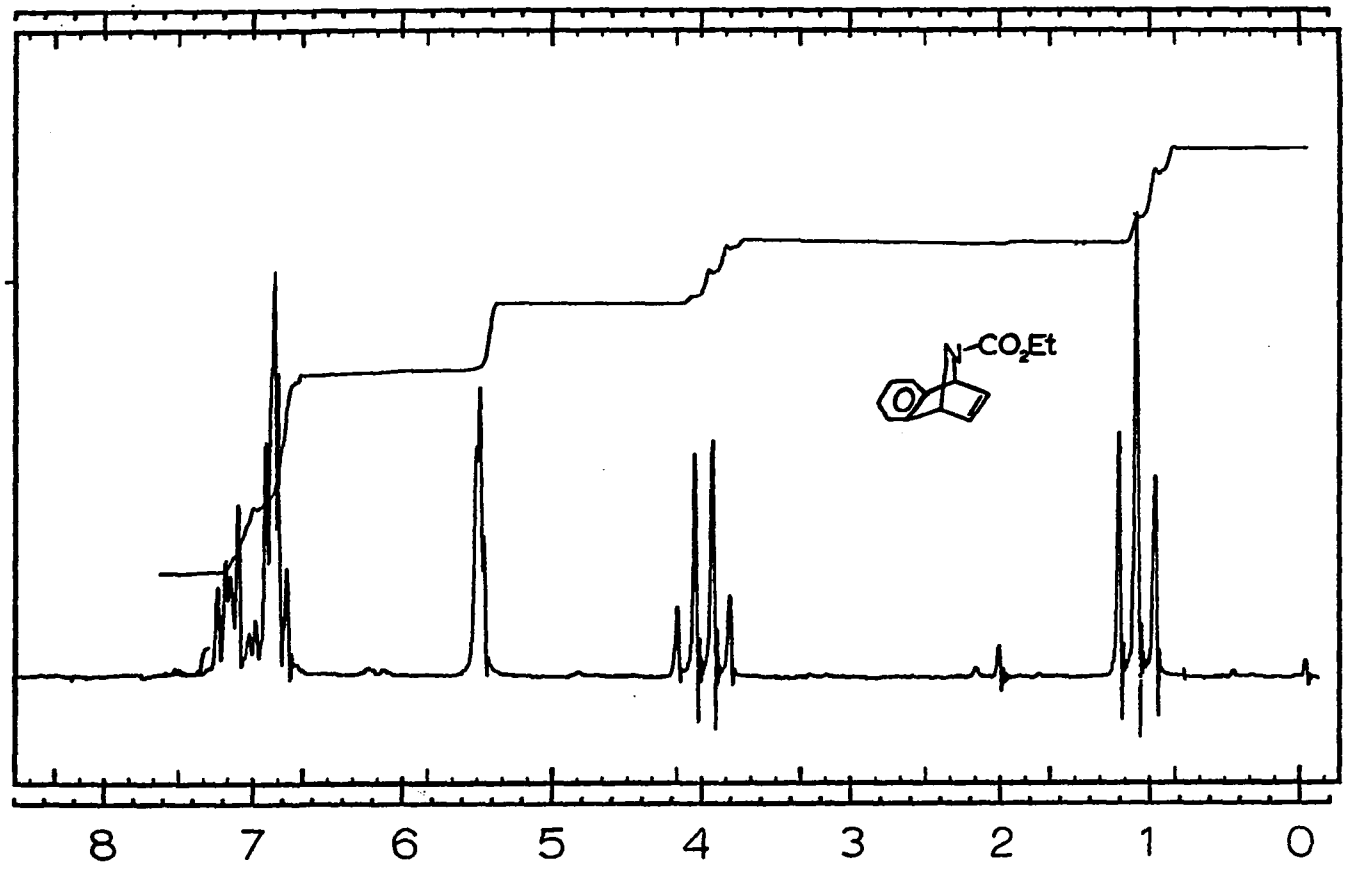


Figure 17. 60 MHz nmr spectrum of L, $CDCl_3$

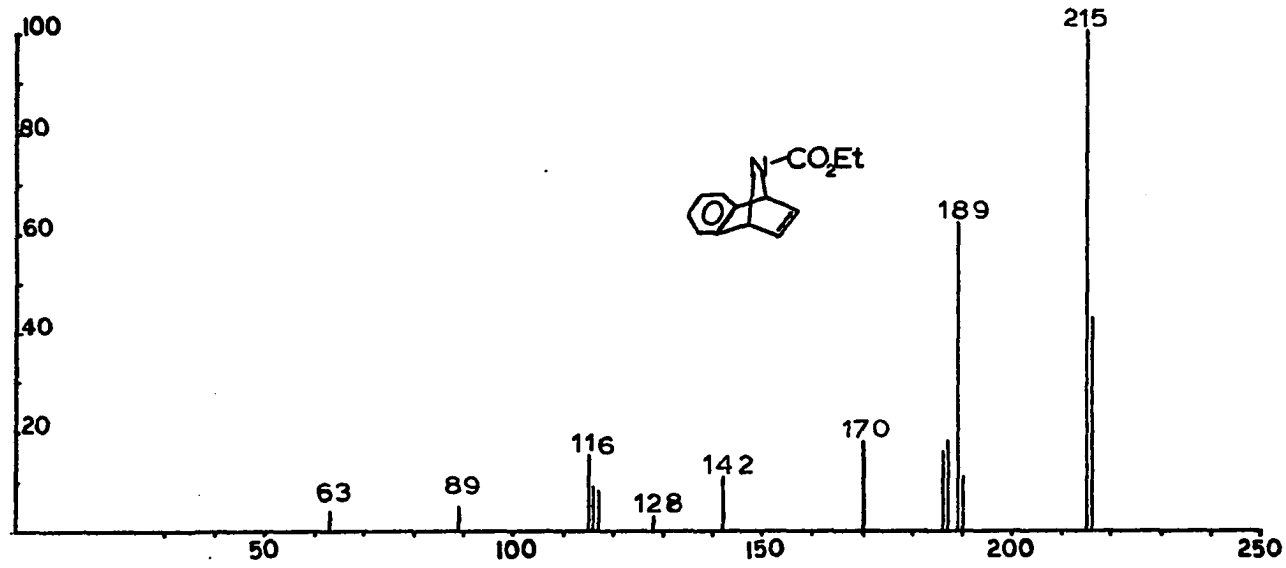
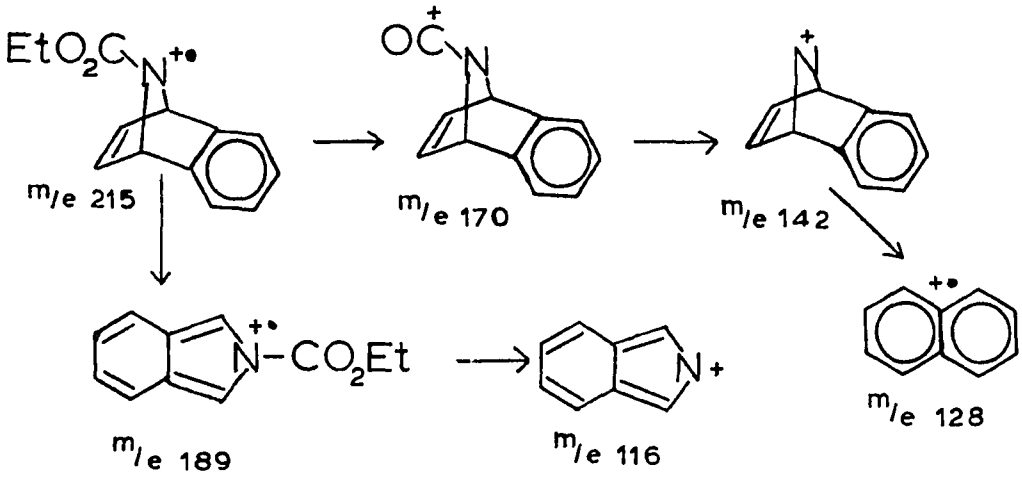


Figure 18. 70 eV mass spectrum of L



Catalytic hydrogenation of L afforded N-carboethoxy-7-azabenzobicyclo(2.2.1)heptene, LI, in nearly quantitative yield. (Catalytic deuteration yields LI-exo,exo-d_2, see part II of this dissertation). The nmr and mass spectra of LI are shown in figures 19 and 20.

The chemical shift assignments listed in the experimental section are corroborated by results of double resonance experiments at 60 MHz: Double irradiation of the multiplet at δ 5.02 (1,4 bridgehead protons) causes partial colapse of the multiplet at δ 2.16 (the exo protons are still split by geminal and vicinal endo protons). Conversely, irradiation of the signal at δ 2.16 causes the multiplet at δ 4.07 to collapse to a "singlet" (broadening of this resonance is probably due to small allylic coupling to aromatic protons). The mass spectrum of LI displays the molecular ion, an ion due to loss of ethylene from the molecular ion, and an ion derived from a McLafferty rearrangement. These ion assignments are substantiated by examining the mass spectrum of LI-exo,exo-d_2:

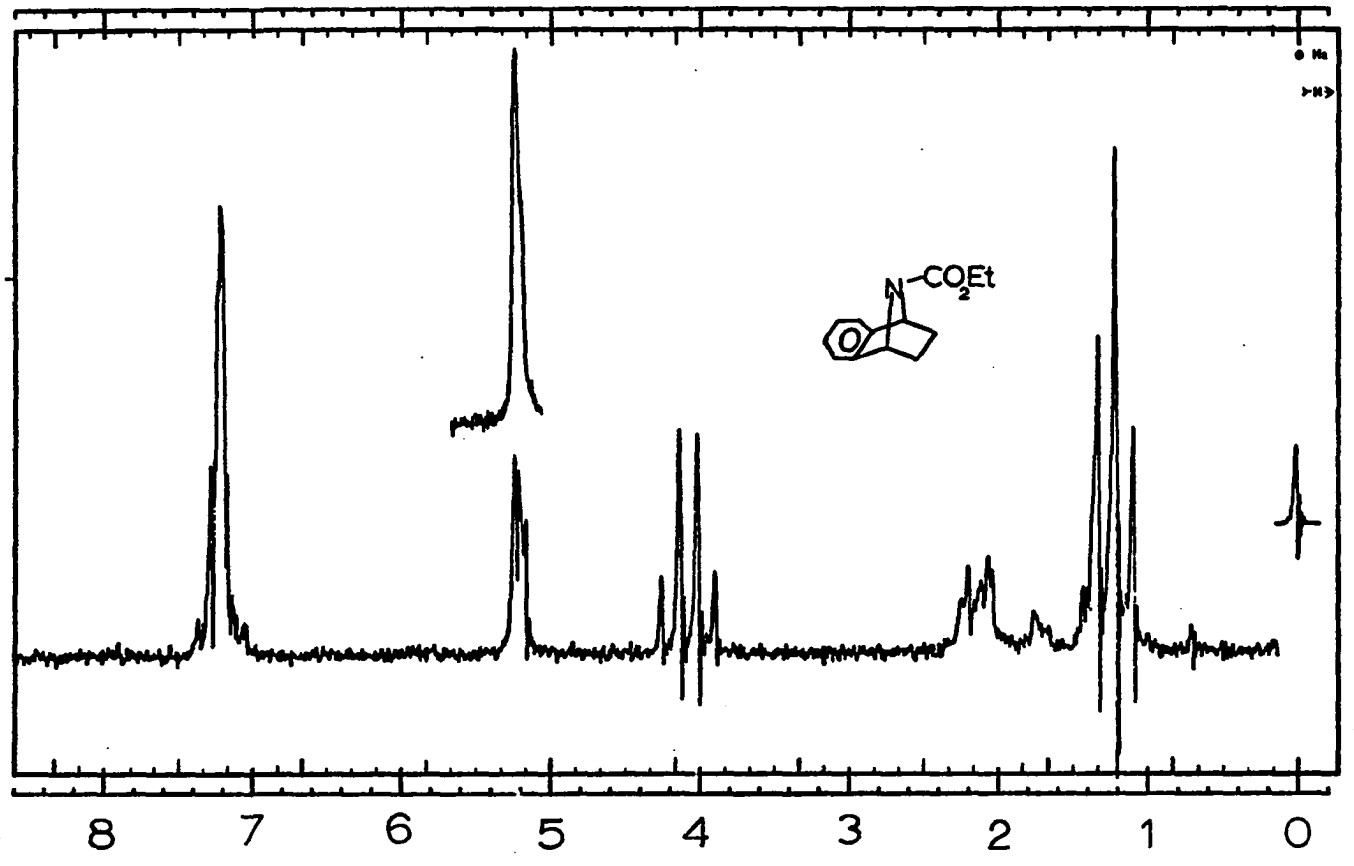


Figure 19. 60 MHz nmr spectrum of LI, $CDCl_3$; offset double irradiation at δ 2.15, observe δ 5.72.

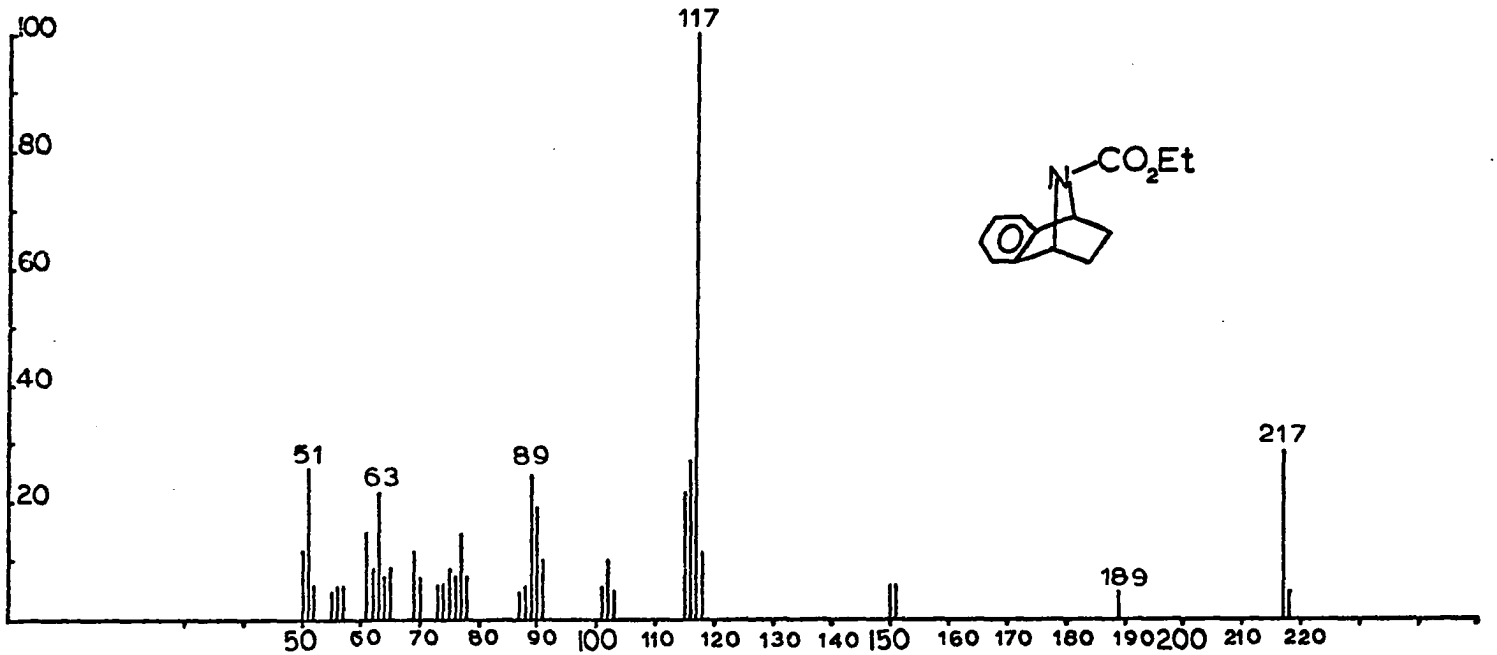
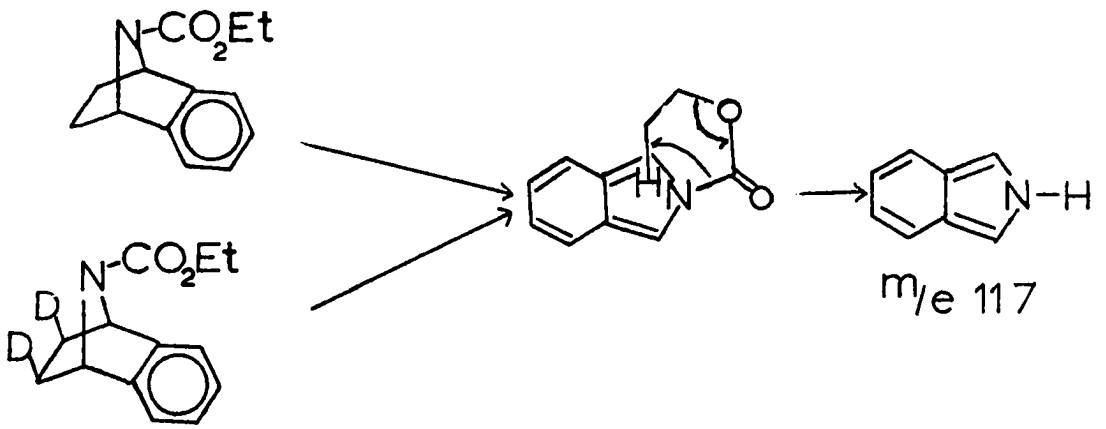


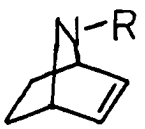
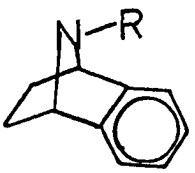
Figure 20. 70 eV mass spectrum of LI



The synthesis of XVII is achieved by treating LI with a slight excess of LAH in refluxing ether for several hours. Sublimation of crude product affords XVII as a waxy solid. The nmr and mass spectra of XVII are show in figures 21 and 22.

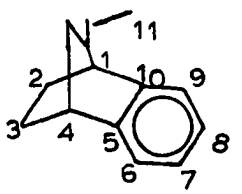
The nmr spectrum of XVII is quite similar to XVI. Generally the chemical shifts of the exo, endo and 1,4 bridgehead protons of 7-azabenzonorbornenes are observed about 0.2 to 0.5 ppm downfield relative to the corresponding absorptions of 7-azanorbornenes. The following Table lists the chemical shift values for 3 pairs of substituted amines.

TABLE III

				Δ
R = Me	exo	1.76	2.13	0.37
	endo	0.98	1.16	0.18
	bridgehead	3.69	4.02	0.33
R = CO_2Et	exo	1.86	2.15	0.29
	endo	1.12	1.27	0.15
	bridgehead	4.75	5.23	0.48
R = H	exo	1.73	1.96	0.23
	endo	1.02	1.18	0.16
	bridgehead	4.13	4.43	0.30

Chemical Shifts in δ, $CDCl_3$ Solution

In addition to the proton nmr of XVII, we also obtained C^{13} nmr. Listed below are the carbon chemical shifts plus one bond JC^{13}-H values.



Carbon	Chemical Shift (ppm downfield of TSM)	$^1J_{C-H}$ In Hertz
1,4	67.4	155, doublet
2,3	26.7	140, triplet
11	35.6	135 quartet
5,10))	121	155 triplet
6,9))	126	155 triplet
7,8)		

It is interesting to note that in this amine the carbon atom hybridization correlates with the $^1J_{C-H}$. As has been shown for hydrocarbons,[108] increased "s" character is reflected in the larger $^1J_{C-H}$ values. For the series C-11, C-2(3), C-1(4) both the predicted "s" character and the magnitude of $^1J_{CH}$ increase. Proximity to the nitrogen atom, an electronegative substituent is <u>not</u> responsible for the observed order. (For an example where the effect of adjacent electronegative sustitutents can't be neglected, see part III of this dissertation and references cited therein).

We have also obtained proton nmr of XVII at 300 MHz. Figure 23 shows the complete proton nmr of XVII (benzene solution). Figures 24 through 26 show expanded portions of the 300 MHz nmr along with the corresponding computer simulated spectra (obtained for the six spin system utlizing a SIMEQ/II computer program)

The mass spectrum of XVII exhibits the characteristic ion due

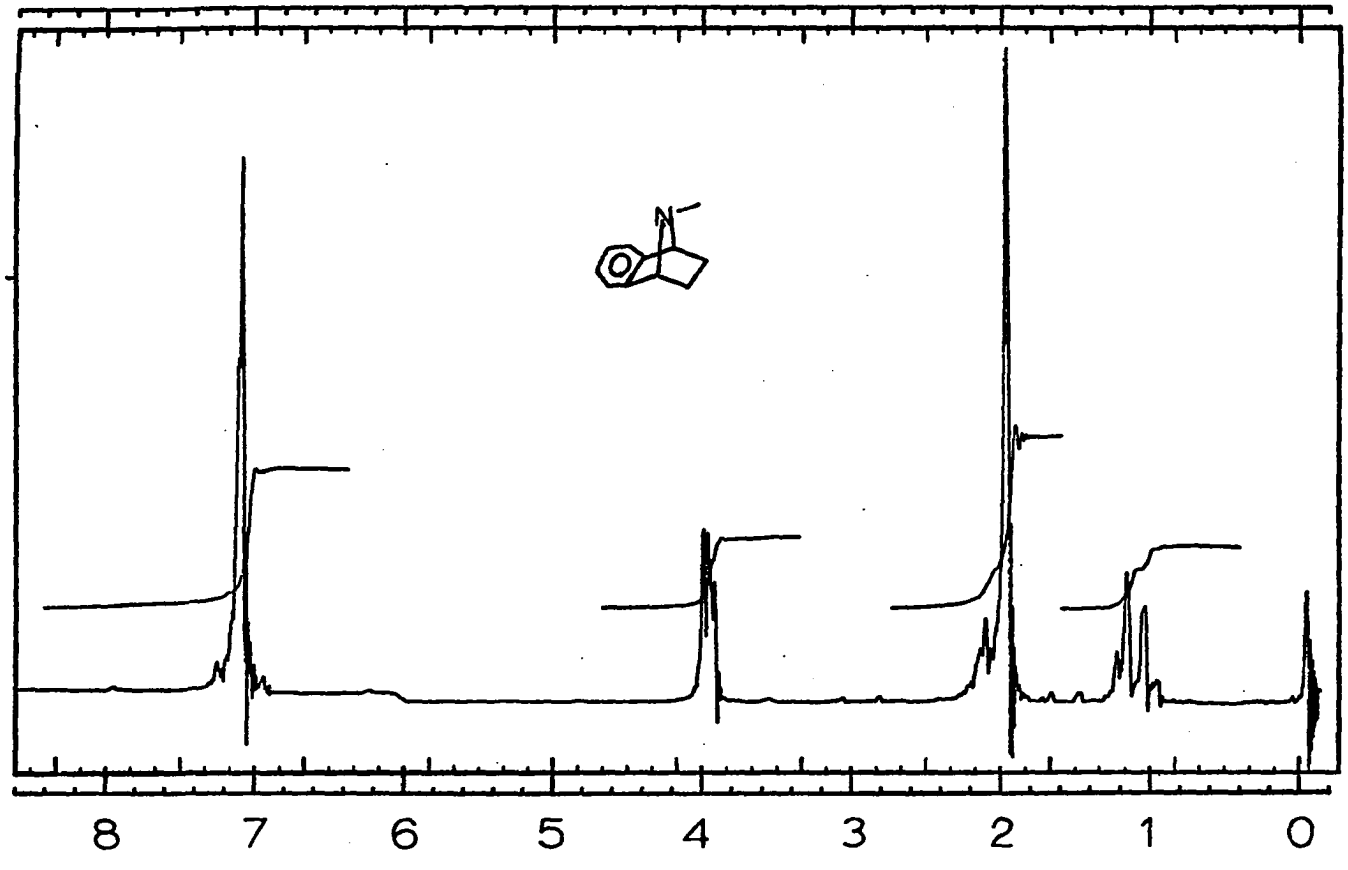


Figure 21. 60 MHz nmr spectrum of XVII, $CDCl_3$

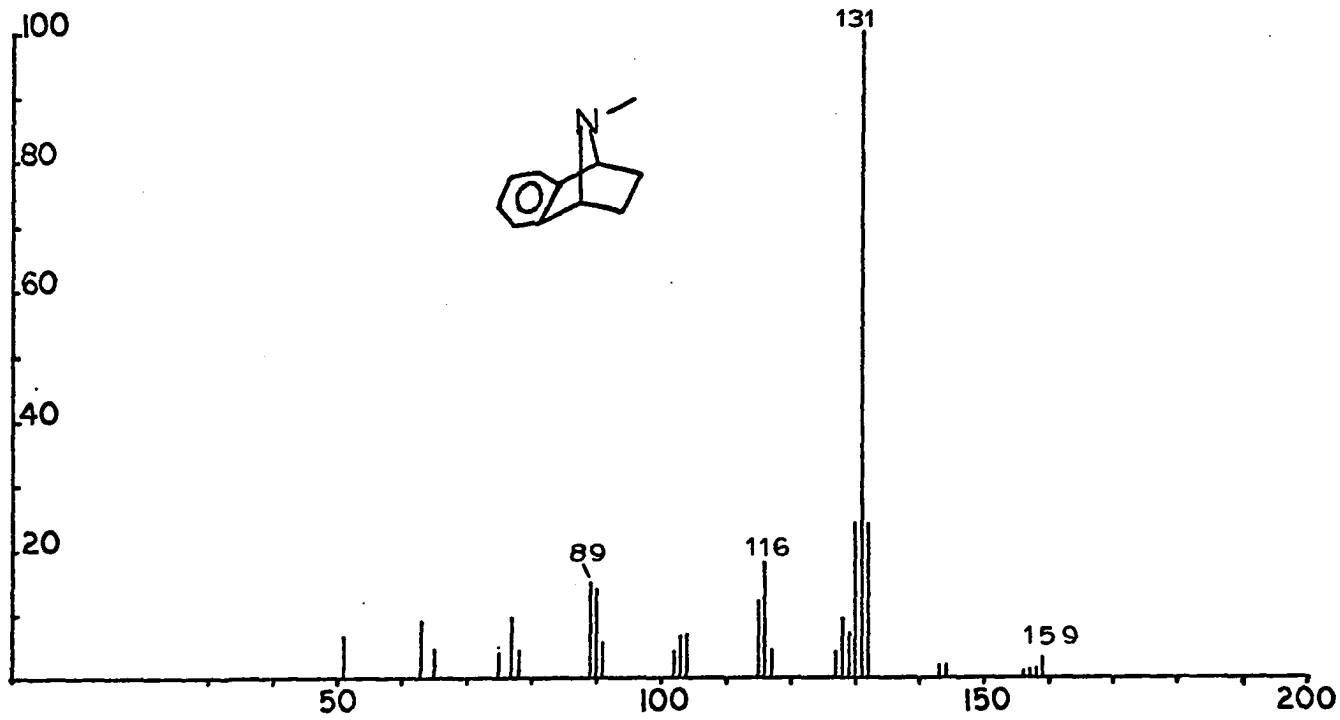


Figure 22. 70 eV mass spectrum of XVII

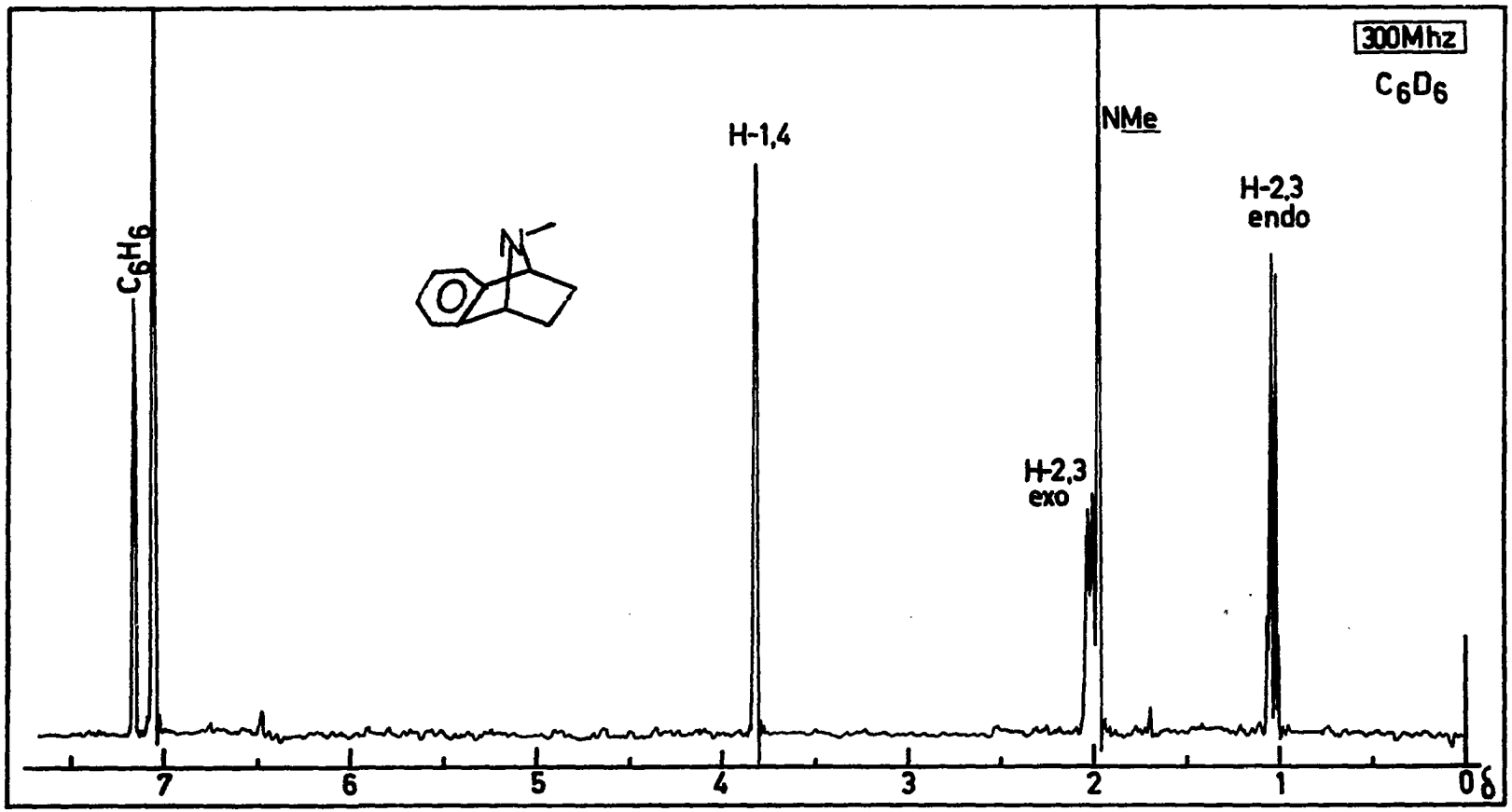


Figure 23. 300 MHz nmr spectrum of XVII, C_6D_6.

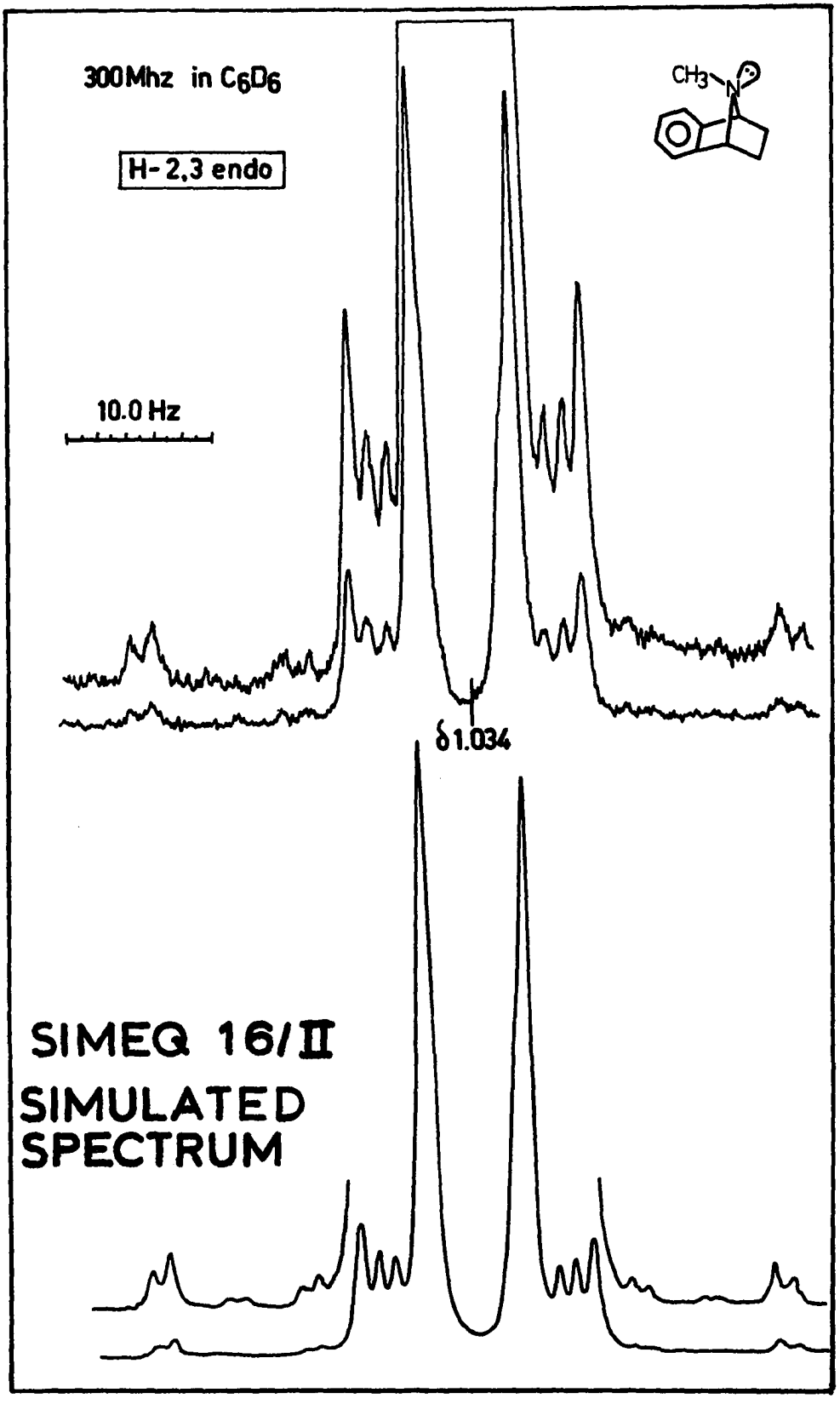


Figure 24. Partial 300 MHz nmr spectrum of XVII, C_6D_6, endo proton region.

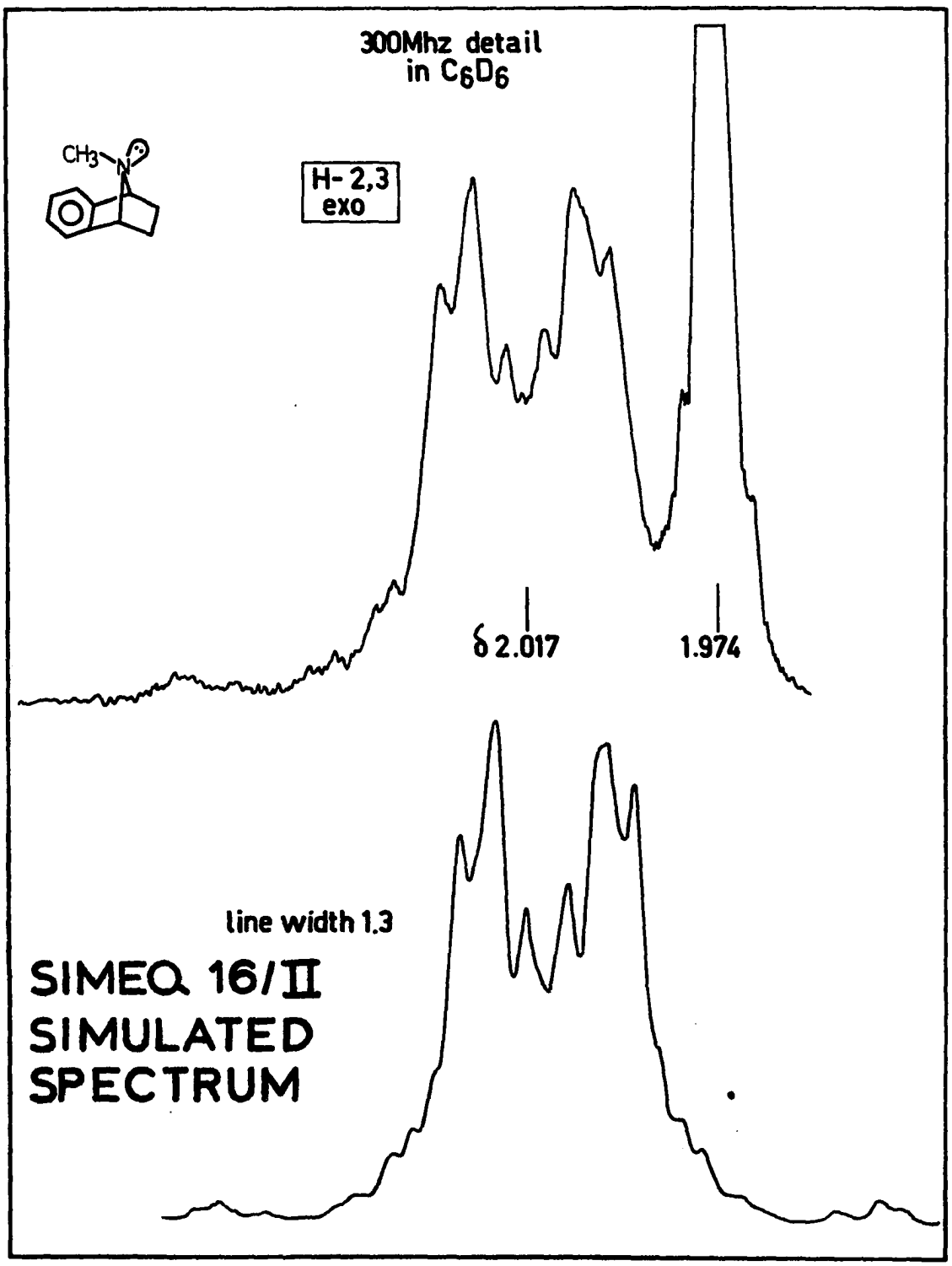


Figure 25. Partial 300 MHz nmr spectrum of XVII, C_6D_6; exo proton region.

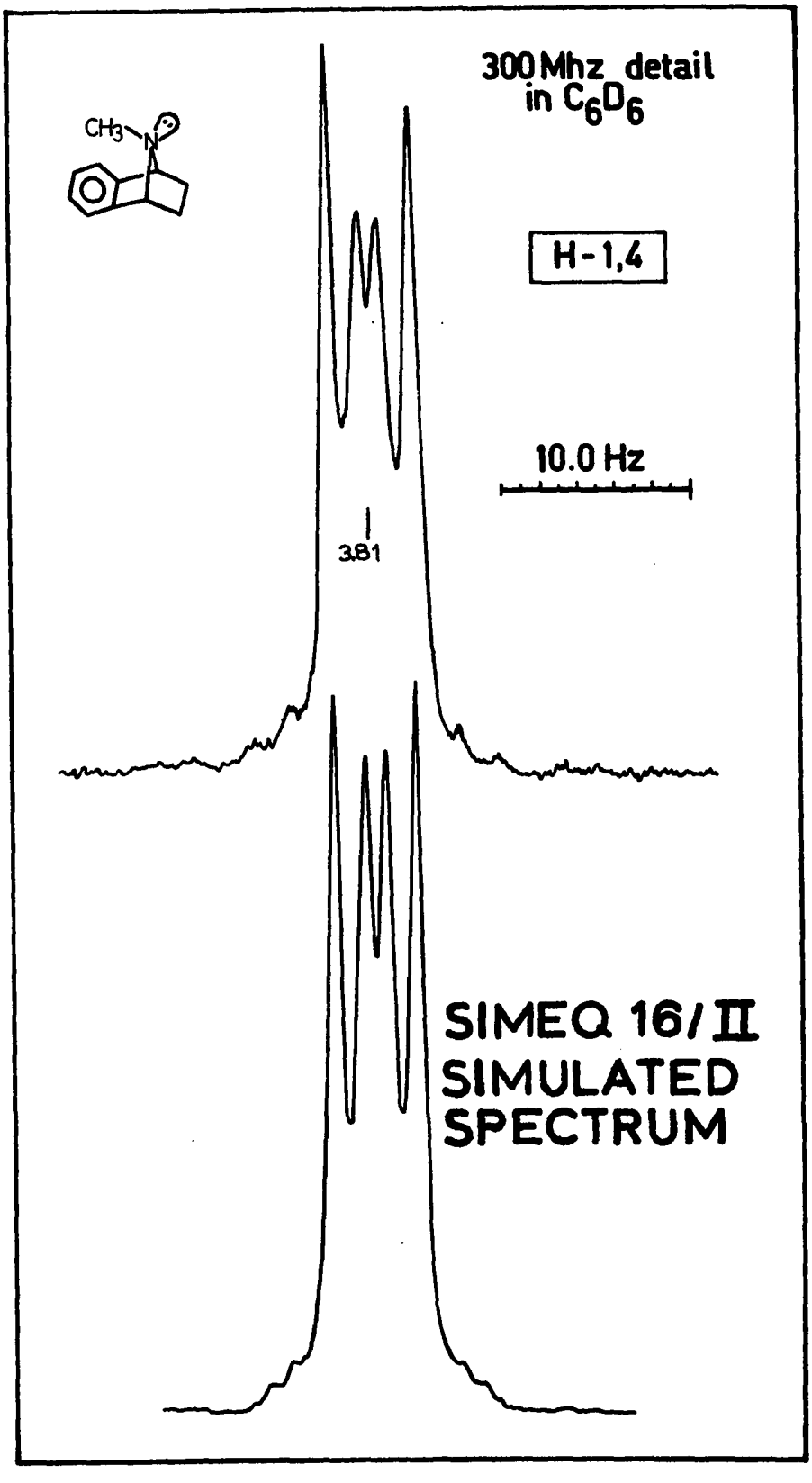
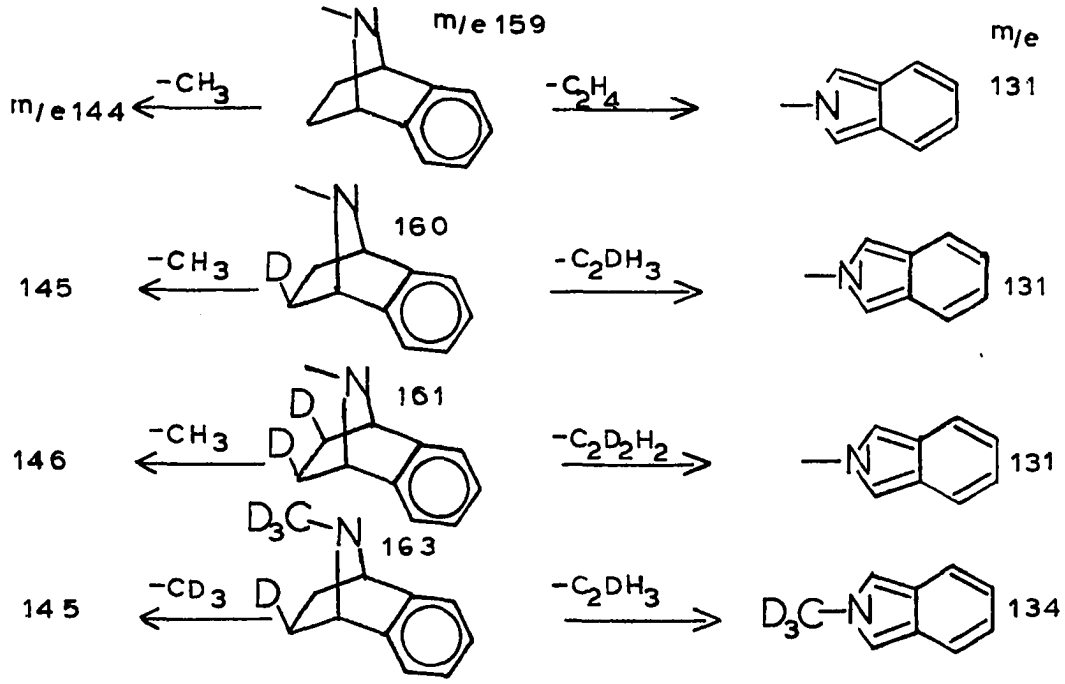


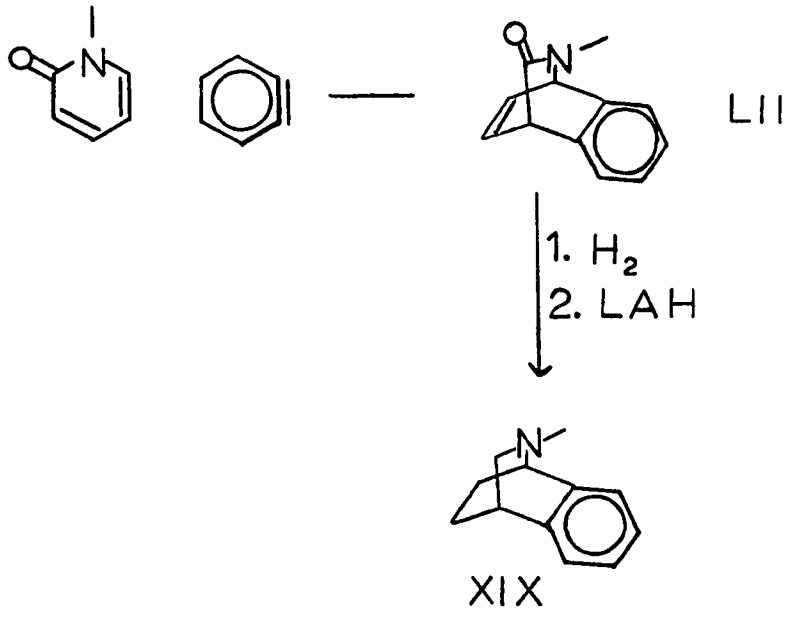
Figure 26. Partial 300 Mhz nmr spectrum of XVII, C_6D_6; bridgehead proton region.

to loss of ethylene. The hypothesized retro-Diels-Alder fragmentation is well supported by examining the spectra of several deuterated analogues of XVII.



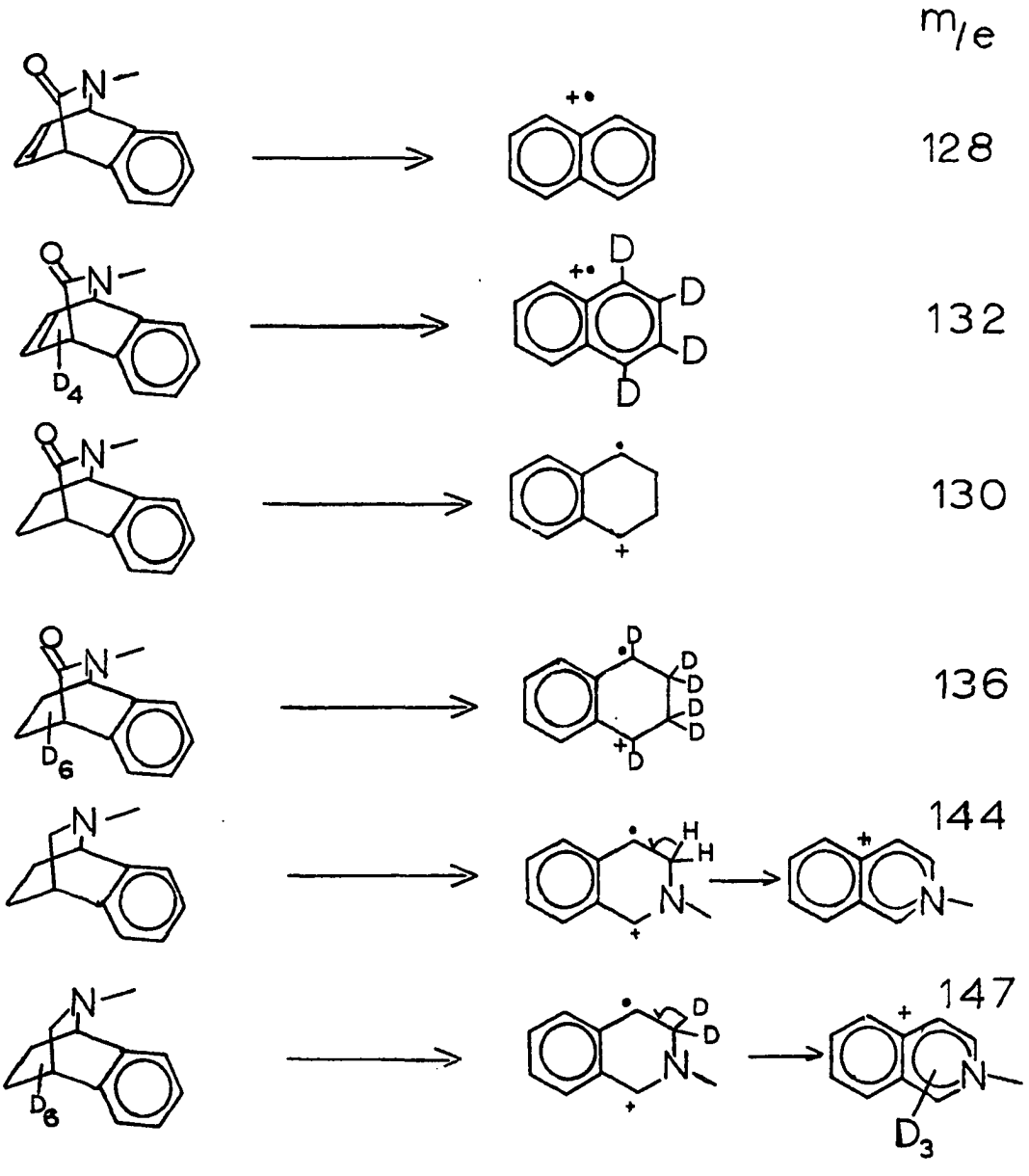
Synthesis of N-Methyl-5-Azabenzobicyclo-(2.2.2)octene (XIX)

Two schemes for the synthesis of XIX were available to us: Cyclization of 1-methylamino 1,2,3,4 tetrahydronaphthlene-9-carboxylic acid[109] and Diels-Alder addition of N-methyl-2-pyridone with benzyne.[110] Due to the ready availability of starting materials, the latter scheme was used. The overall synthesis of N-methyl-1,4-ethano-1,2,3,4-tetrahydroisoquinoline,[111] XIX, is outlined below.



The synthesis of LII has been described previously.[110] We adopted a similar procedure, with the following exception: In Scheinen's procedure,[110] benzyne was generated from anthranilic acid and isoamyl nitrite (in situ preparation of benzenediazonium-2-carboxylate). In our hands this procedure led to a product which was always contaminated with isoamyl alcohol. To avoid this, benzenediazonium-2-carboxylate was prepared in a separate reaction.[112] The salt thus prepared was combined with an equilmolar amount of N-methyl-2-pyridone in refluxing THF. Our product had physical[110] and spectral[113] data consistent with those for known LII. Catalytic hydrogenation of LII afforded LIII in good yield. Conversion of LIII to XIX was effected in 85-90% yield by reduction of LIII with lithium aluminum hydride in refluxing ether. The corresponding deuterated compounds, LII-d_4, LIII-d_6, and XIX-d_8 were obtained via N-methyl-2-pyridone-d_4, catalytic deuteration and reduction with lithium aluminum deuteride. The nmr and mass spectra of XIX are shown in figures 27 and 28. A common feature of the mass spectra of LII and LIII and their deuterated analogues is the base peak which

corresponds to loss of the carbon-nitrogen bridge from the molecular ion. For XIX and its deuterated analogue, the base peak corresponds to an ion formed via loss of the ethylene bridge, followed by loss of H·(D·) to give an aromatic cation.



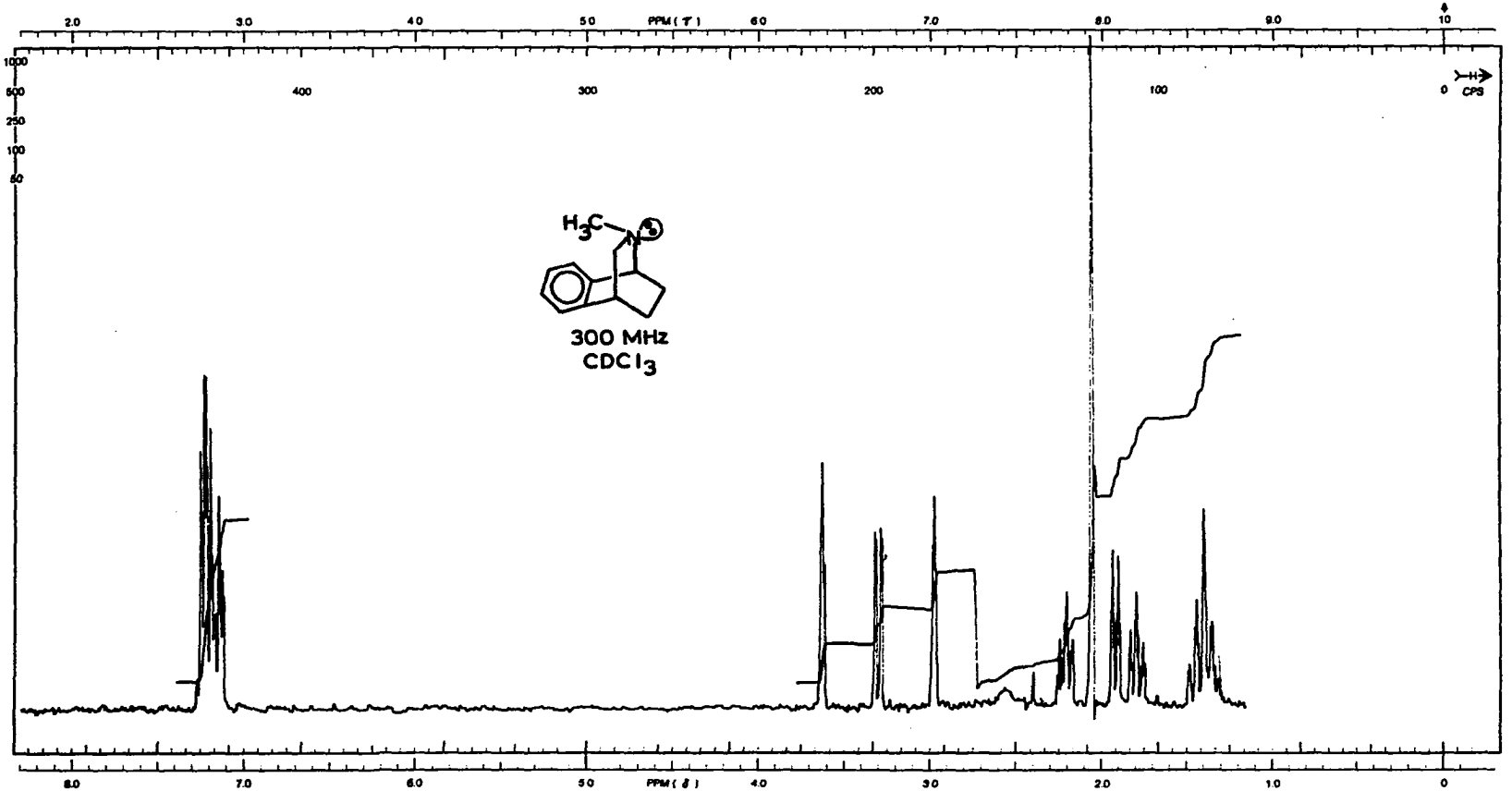


Figure 27. 300 MHz nmr spectrum of XIX, $CDCl_3$.

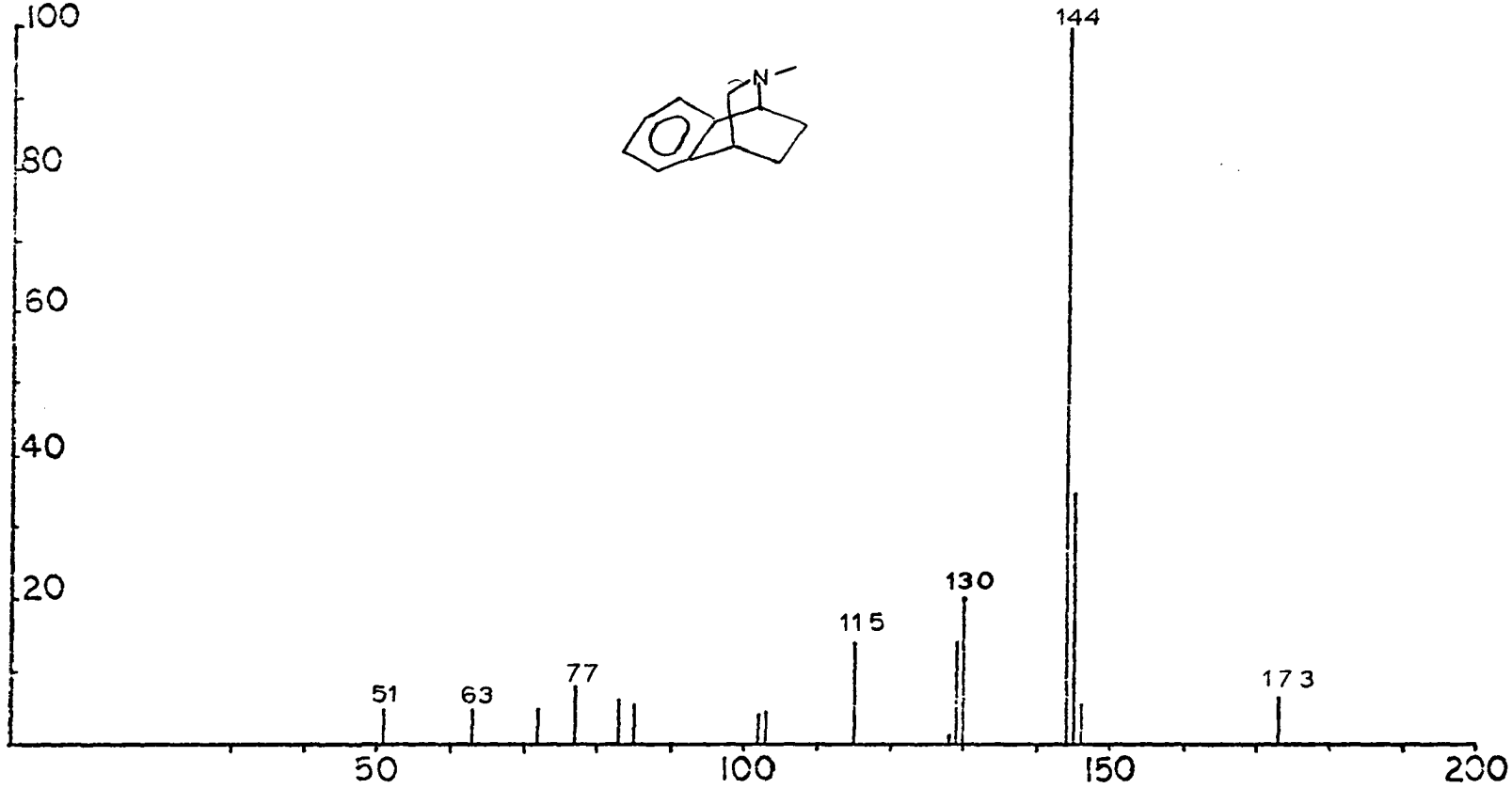
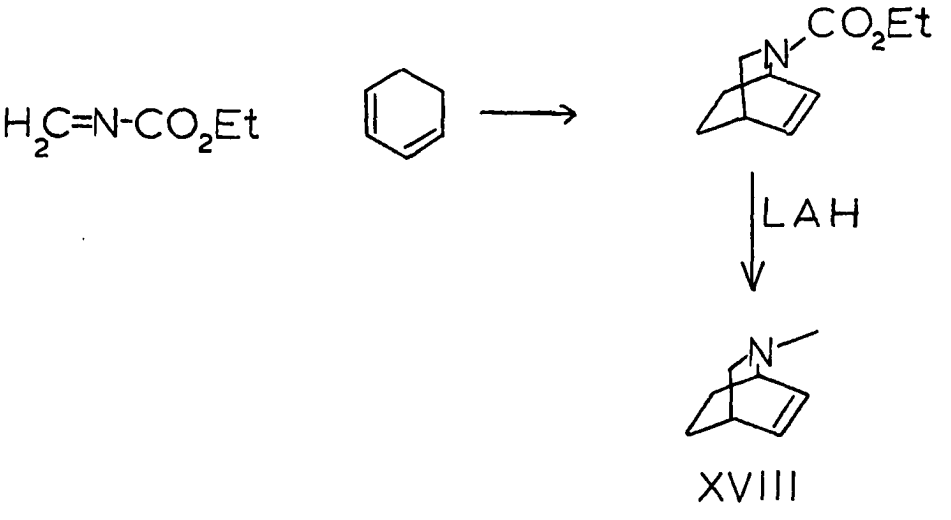


Figure 28. 70 eV mass spectrum of XIX

Synthesis of N-methyl-5-azabicyclo(2.2.2)octene (XVIII)

The procedure of M. P. Cava et al.,[58] was employed for the synthesis of XVIII. Treatment of methylene-bisurethane with boron trifluoride etherate generates the N-carboethoxy imine.[114] This material subsequently reacts with 1,3 cyclohexadiene to afford the Diels-Alder adduct. Lithium aluminum hydride reduction of the carbamate affords N-methyl-5-azabicyclo (2.2.2)octene in an overall yield of 25%.



XVIII

Results

As discussed previously, to determine the equilibrium constants for XVI through XIX, it is necessary to observe the nmr specta under conditions of slow exchange. An exchange process is slow relative to the nmr time scale when the first order rate constant at coalesence, k_c, is about twice the frequency difference of the exchanging sites:

$$A \rightleftharpoons B \qquad k_c = \frac{\pi}{\sqrt{2}}(\nu_a - \nu_b)$$

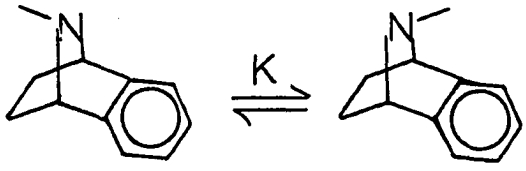
where

k_c = rate constant

ν_A, ν_B are the Chemical Shifts of protons at sites A and B

Strictly speaking, this expression is only applicable for exchange in two equally populated sites.[42,115] However, comparison of this approximation with full line shape analysis[116-118] suggests that it may be a reasonably good approximation if $\Delta\nu > 2$ Hz and K_{eq} is between 0.3 and 3. The approximation is especially useful when employed in the calculation of free energies of activation, $\Delta G^{\ddagger}$, at the coalesence temperature. Generally, the error introduced by use of this approximation is no worse than the error inherent in curve fitting methods.

The first compound examined by dynamic nmr spectroscopy was XVII. In $CDCl_3$, CCl_2F_2, or $C_2H_2F_2Cl_2$ no change could be observed in the 100 MHz nmr spectrum down to 223° Kelvin.[119] However, we suspected that this might be due to an artifact, i.e., at 100 MHz, the resolution is not sufficient to observe the two slowly exchanging invertomers. Our suspicions were confirmed upon examination of the dynamic nmr spectrum of XVII-d_2 (see figure 29a,b). The absence of exo protons in XVII-d_2 allows observation of the N-methyl resonances of both major and minor invertomers. At ca. 273° coalesence broadening of the N-methyl resonance begins. Broadening increases to about 253°, then on further cooling the spectrum sharpens. At 233° two distinct signals are observed, which correspond to the N-methyl resonances. The less intense singlet (6%) was 21 Hz downfield of the more intense singlet (94%). Similar results were obtained for XVII at 300 MHz. Assuming the net anisotropy effects are the same in N-methyl-7-azabenzonorbornene and the carbocyclic analogues, syn- and anti-7-methyl-benzonorbornene,[57] allows a comparison of the relative chemical shifts. The more intense resonance upfield corresponds to XVIIb being the more stable. Figure 30 shows the 300 MHz nmr spectrum of XVII at 233°.



$$K = \frac{94}{6} = 15.7$$

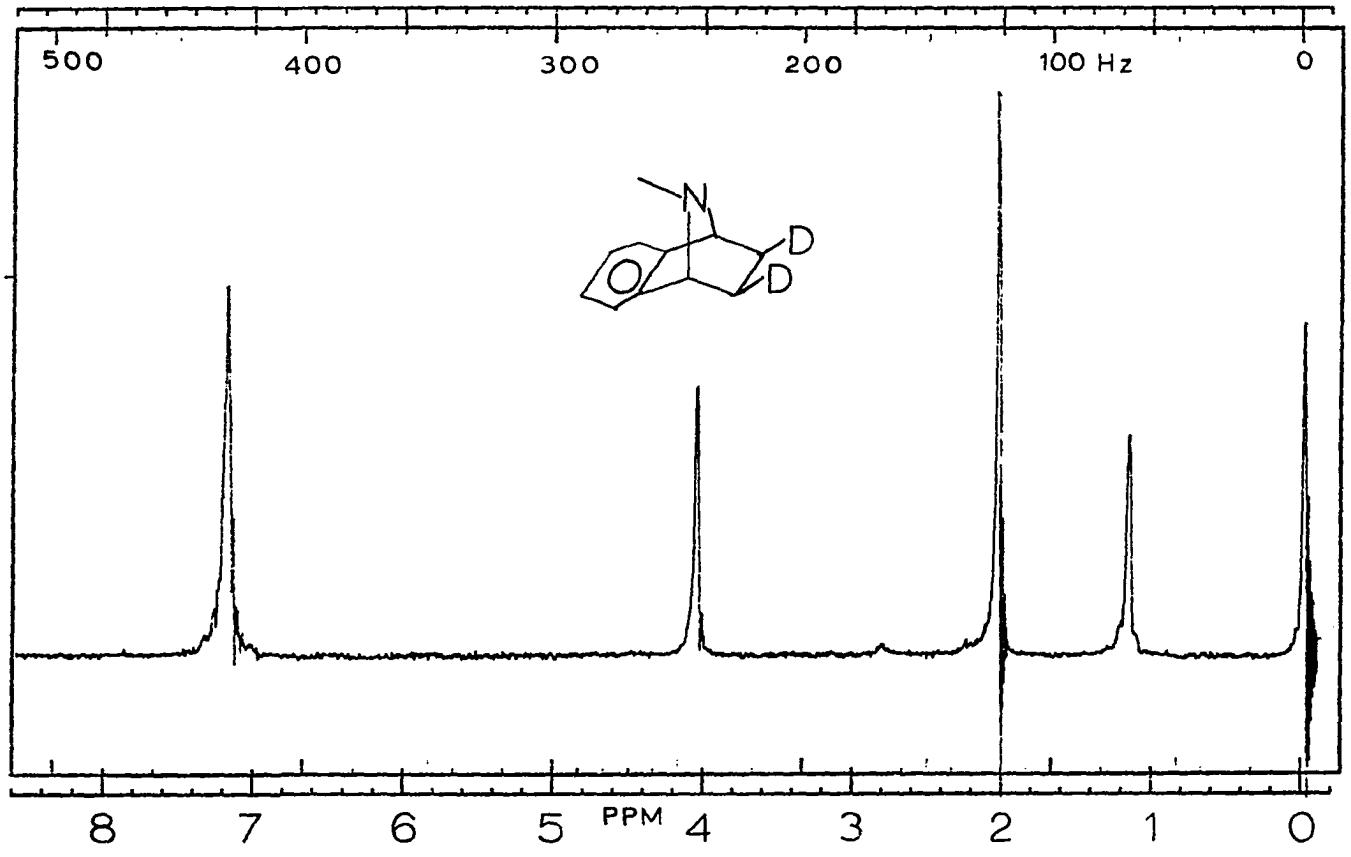


Figure 29a. 60 MHz nmr of XVII-d_2, $CDCl_3$

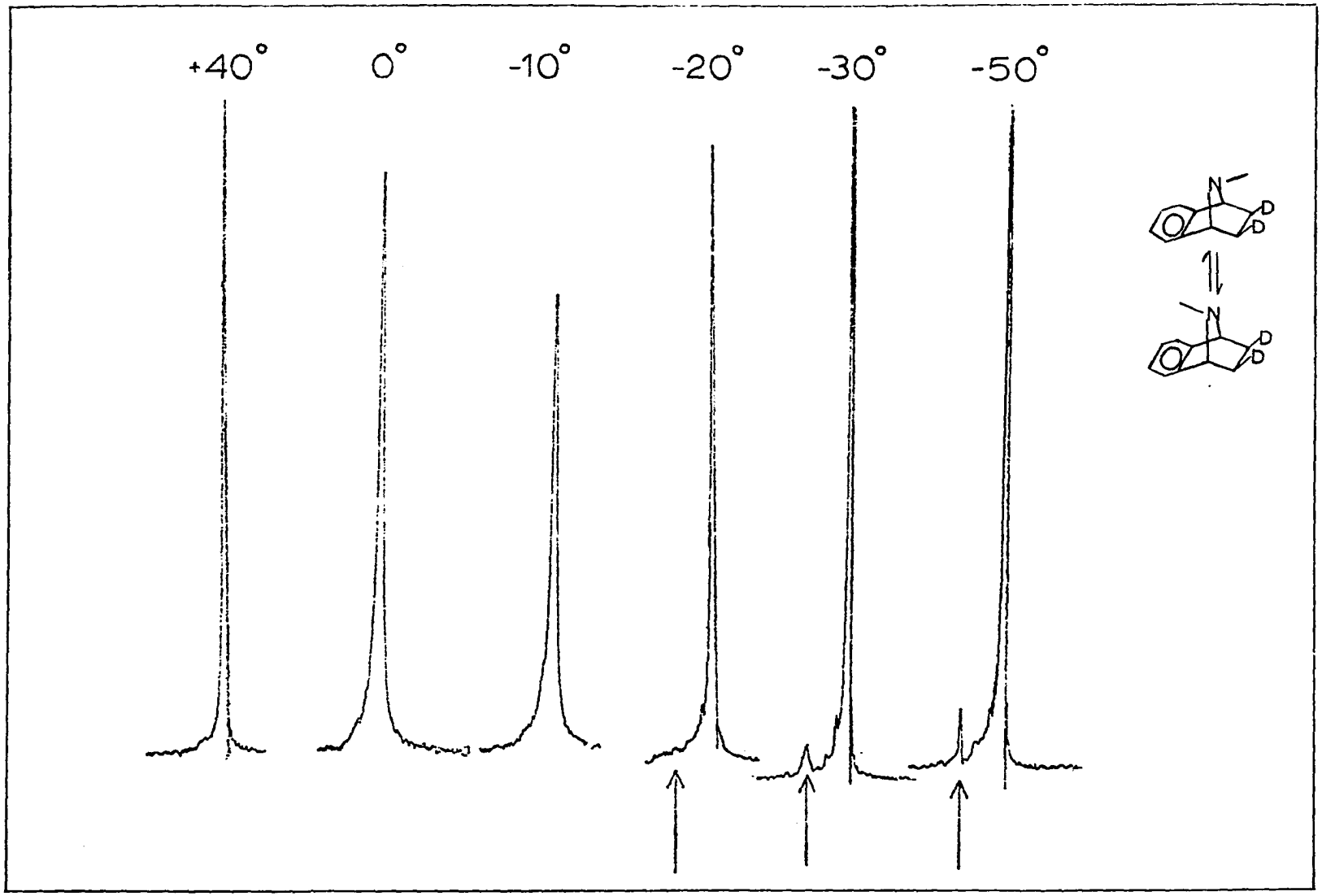


Figure 29b. N-Methyl resonance (100 MHz) of XVII-d_2 at various temperatures; the arrows indicate the position of the N-methyl resonance of the minor invertomer.

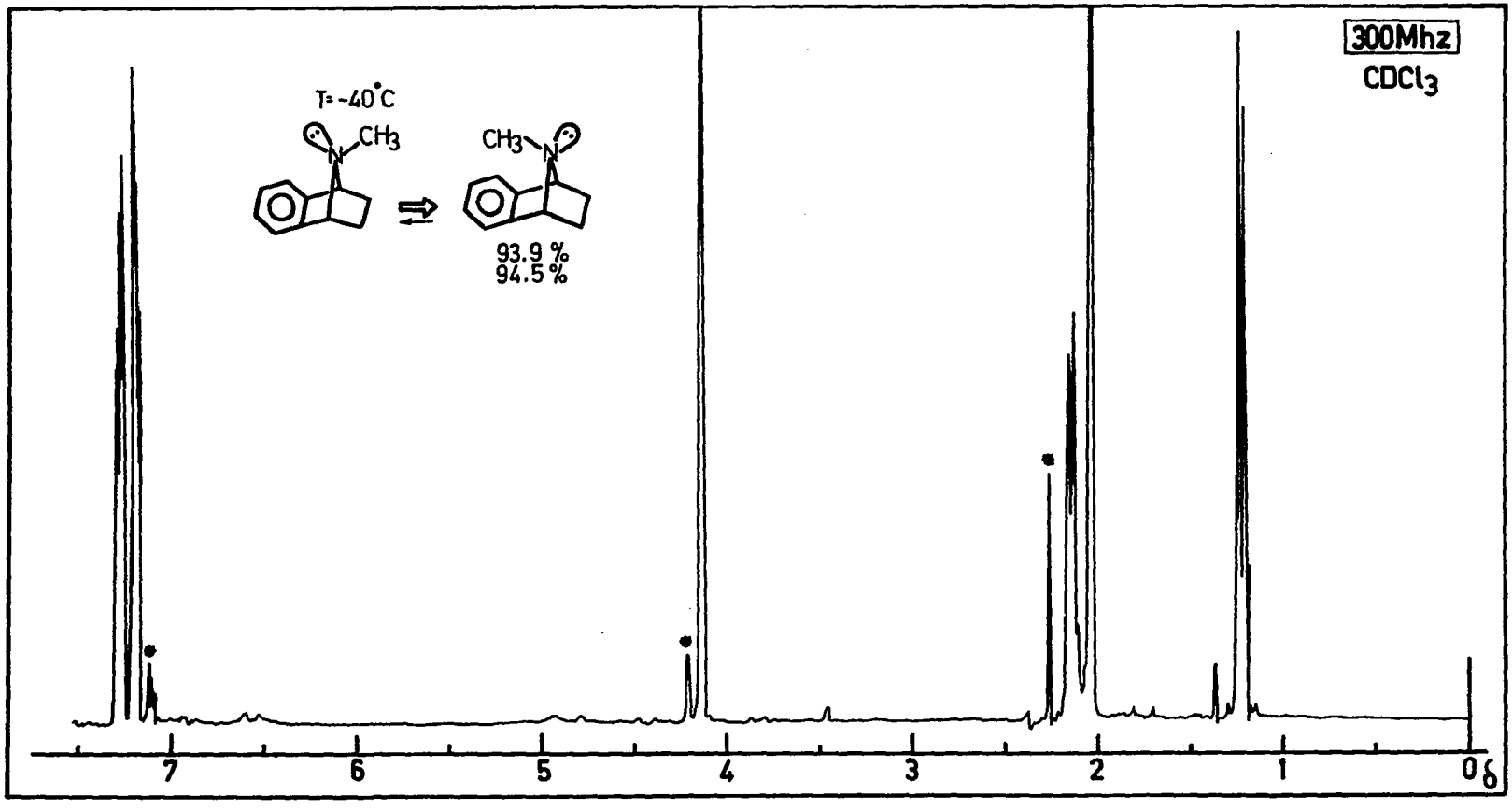


Figure 30. 300 MHz nmr spectrum of XVII at 233°K, $CDCl_3$.

Application of the rate constant approximation using 253° as the coalesence temperature yields:

$$k = 47\,sec^{-1}$$

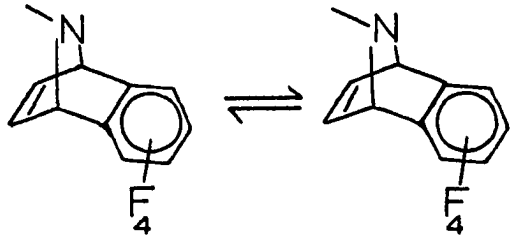
This value can be substituted into the Eyring equation[120] to obtain the activation energy, $\Delta G^{\ddagger}$, at 253°

$$\Delta G^{\ddagger} = -RT\ln\left[\frac{hk_c}{k_B T}\right]$$

$$\Delta G^{\ddagger} = 13\ kcal/mole$$

where k_B = Boltzman's Constant
h = Plancks Constant
R = Gas Constant
k_c = Rate Constant
T = Temperature in °K

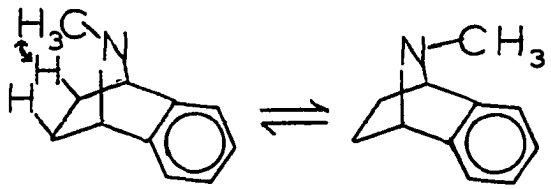
Although the ratio XVIIa/XVIIb is far from unity, the result of $\Delta G^{\ddagger}$=13 kcal/mole is in good agreement with that found by Gribble and coworkers[54] for LIV.



$\Delta G^{\ddagger}$=14 kcal

Compound LIV is more strained than is XVII due the presence of the additional double bond. The greater strain in LIV is reflected in its slightly larger activation energy for nitrogen inversion. (the shorter C_5-C_6 bond decreases angle C_1-N-C_4, thus destabilizing the sp^2 hybridized transition state.

Thermodynamic results from the temperature dependent nmr experiment with XVII agree with our predictions; that is, invertomer XVIIa with the nitrogen lone pair syn to the π system is destabilized relative to the corresponding invertomer in which the lone pair is <u>anti</u> to the π system. We had suggested that this might be due to bishomoantiaromatic interaction of the nitrogen lone pair electrons of invertomer XVIIa. Other factors perturbing the equilibrium position are of steric origin. A type of B-strain is present in XVII due to Van der Waals interaction between the <u>exo</u> protons and the methyl group in XVIIa. In XVIIb, the corresponding interaction exists between the <u>exo</u> protons and the nitrogen lone pair electrons. The relative importance of two opposing forces has been termed "conformational rivalry."[121] To determine the relative importance



of steric and electronic effects (here <u>electronic</u> refers specifically to antiaromatic destabilization of XVIIa) it was necessary to obtain data on the relative "size" of $-CH_3$, -H, and lone pair electrons.

Molecular Kerr constant measurements[122] on N-methyl piperidine and piperidine suggested that about equal amounts of axial and equatorial N-methyl piperidine existed in neat solution. For piperidine itself, Kerr constants indicated almost exclusive axial N-H! The suggested steric order, Me~lone pair>H, initiated a hotly contested debate which continues to this day. Calculations based on Van der Waal's radii,[123] and quantum mechanical considerations[124](lowest energy path for approach of a helium atom to ammonia is along the axis of the lone pair electrons) yielded a different order: Methyl>H> lone pair. Subsequent dipole moment and microwave[124] studies strongly support the latter ordering. Recently, nmr results [125] based on the coupling constants of axial and equatorial α protons revert support back to the original Kerr constant order. These results are highly suspect because the possible anisotropy effect of the lone pair electrons on the coupling constants of the α protons was completely ignored. The latest word, with several supporting references, comes from dipole moment studies performed by Katritzky and coworkers.[126] Their results support the order Me>H> lone pair.

For obvious reasons we sought a direct measure of the steric contribution to our observed equilibrium. One method which pertains to conformational rivalry between-Me and -H involves the examination of the nmr spectrum of XVII in acidic media. The free energy difference, ΔG°, between XVIIa and XVIIb is the result of a combination of factors. We can therefore write $\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Electronic} + \Delta G^{\circ}_{Steric}$. An approximation of ΔG°_{s} is that obtained from the equilibrium XVIIa-H^{+} XVIIB-H^{+}. Of course when the nitrogen is protonated there can be no "electronic" component to the free energy difference. Observation of the nmr spectrum

of XVII-H^+ obtained by addition of XVII to 20% trifluoracetic acid (TFA) in $CDCl_3$ indicated an equilibrium constant identical to that of the free base. (Fig. 31) Reexamination of the spectrum after two weeks storage at room temperature showed no change whatsoever. Similarly, addition of XVII to dilute HCl solution yielded nmr spectra of protonated XVII which were unchanged with time, but with a considerably small equilibrium constant.

Table IV lists the equilibrium constants for XVII and XVII-d_2 under various conditions. The more stable invertomers are shown.

We initially assumed that both systems were at equilibrium, and, that the differences in the equilibrium constants were due to solvent effects.[127] This assumption was later challenged by the results of a related pH dependent nmr experiment. The hydrochloride salt of XVII-d_2 was prepared by passing HCl gas through a solution of XVII-d_2 in ether. The precipitate which formed was filtered, dried <u>in vacuo</u>, then dissolved in H_2O. The nmr spectrum obtained immediately thereafter indicated an equilibrium constant of 12! The spectrum gradually changed over a several hour period until the equilibrium constant equaled 1.7. Figure 32 shows the N-methyl and <u>endo</u> proton resonance under four conditions: a) immediately after addition of XVII-d_2·HCl to H_2O (pH <u>ca</u> 5), b) same solution after 24 hours at room temperature, c) XVII-d_2·HCl in conc. HCl solution, d) after previous solution was made basic then reacidified (pH<<1). Pairs of doublets are observed in Figure 32c and d because proton exchange at nitrogen is very slow with respect to the nmr time scale, hence spin coupling is observed. At relatively high pH, proton exchange is rapid (Figure 32a and b) and no spin coupling is observed.

In retrospect, the difference in observed equilibrium constants is simply understood; those solutions whose spectra indicated very

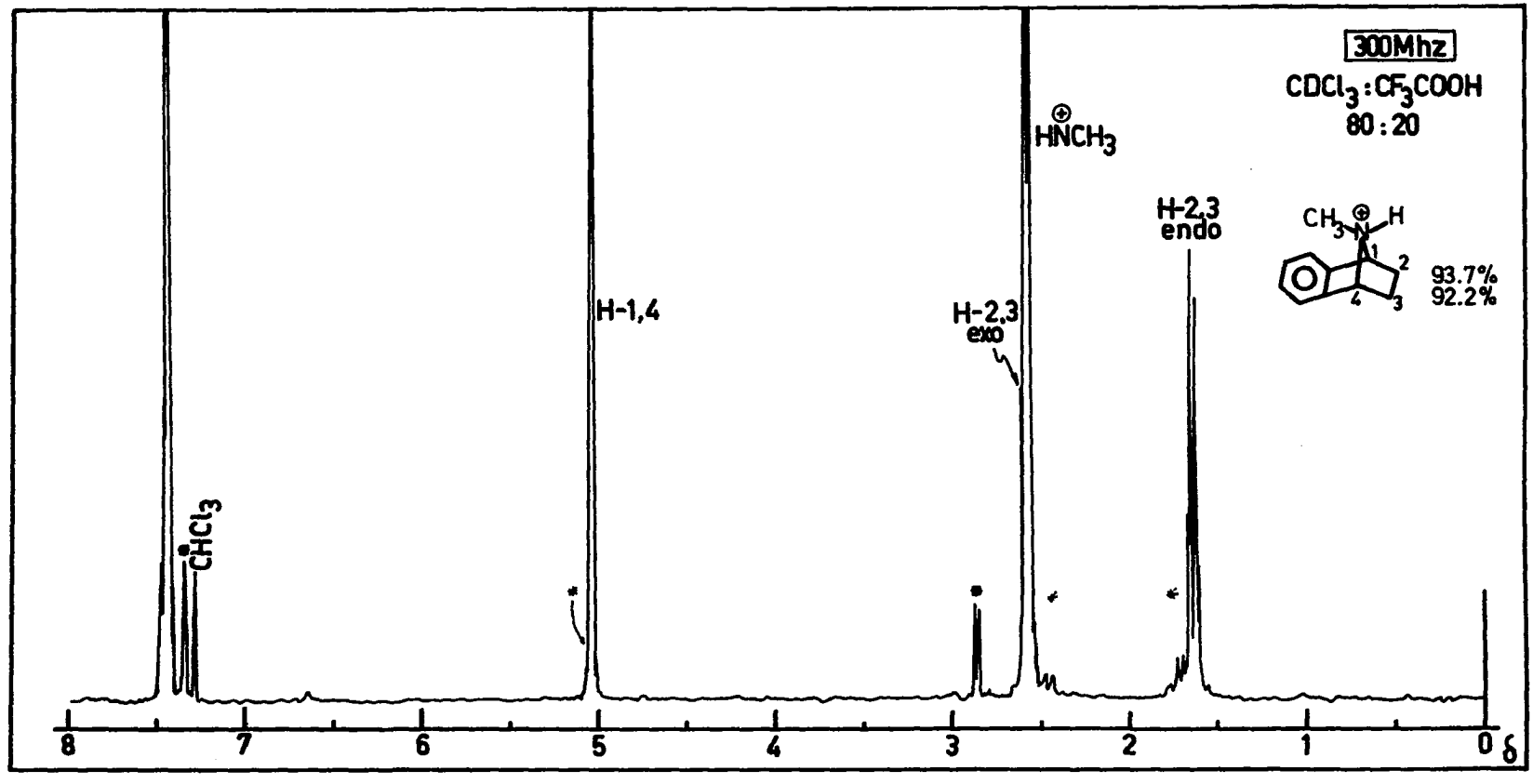
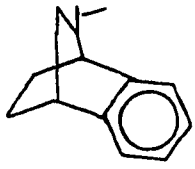
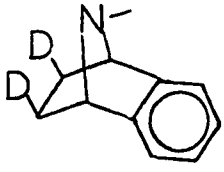
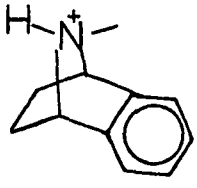
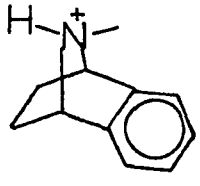
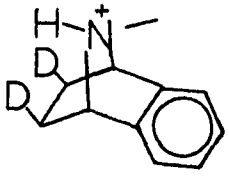
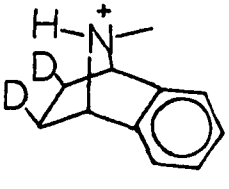


Figure 31. 300 MHz nmr spectrum of XVII-H^+, 80% $CDCl_3$: 20% CF_3COOH

TABLE IV

Compound	Keq	$-\Delta G°(T)$	Conditions
	16.2	1.3 (-40°)	$CDCl_3$ solution
	17.1	1.32 (-40°) ($\Delta G^{\ddagger}$ = 12 kcal)	$CDCl_3$ solution
	13.3	1.53 (25°)	TFA/$CDCl_3$ non-equilibrium
	3	0.51	TFA/$CDCl_3$ equilibrium
	12.7	1.51 (25°)	HCl solution non-equilibrium
	1.72	0.32	HCl solution equilibrium

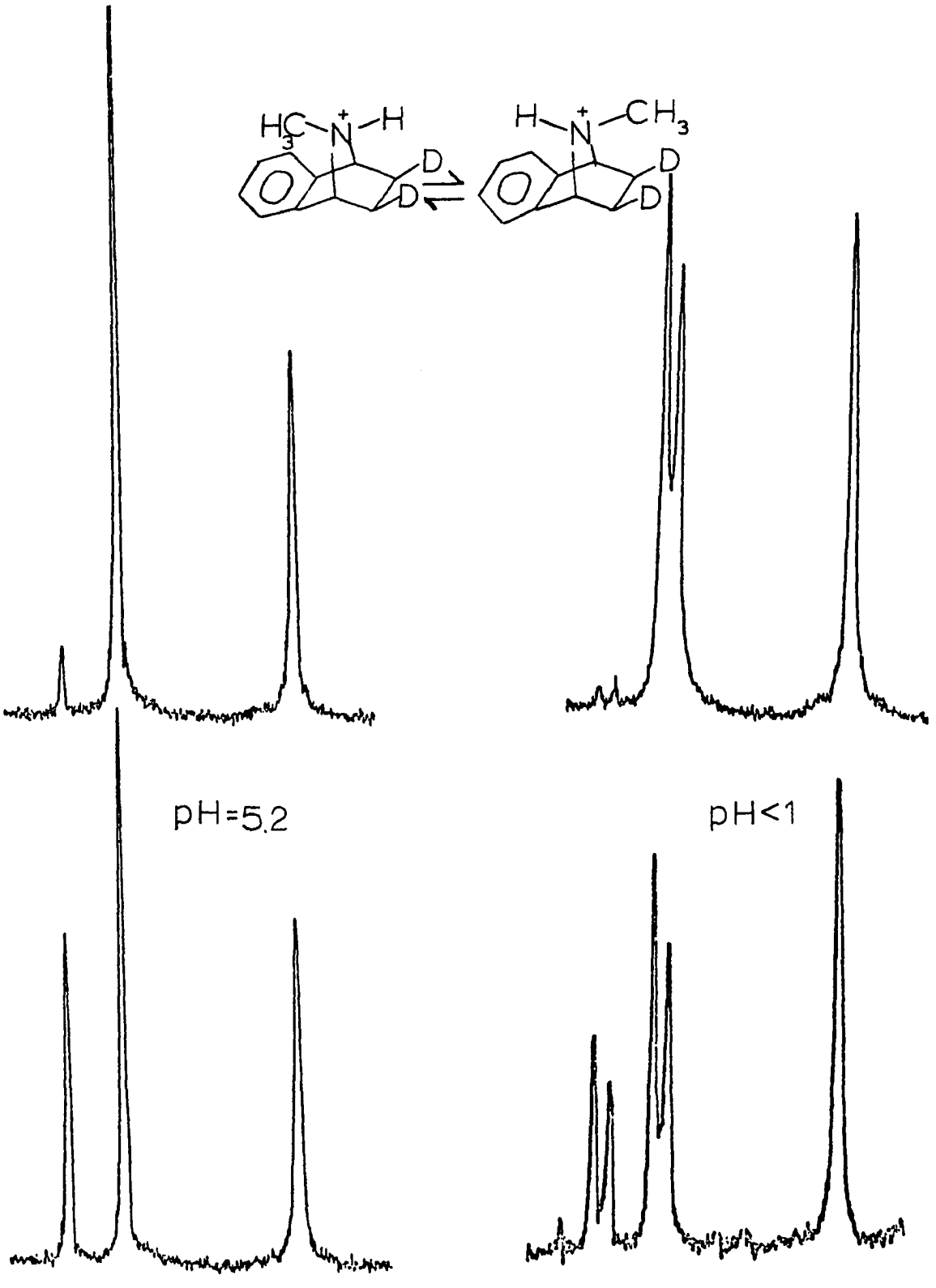


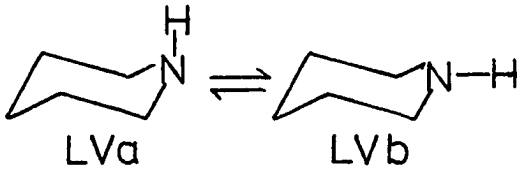
Figure 32. Partial 60 MHz, nmr spectra of protonated XVII-d_2: (a) non-equilibrium conditions, fast exchange; (b) equilibrated, fast exchange; (c) non-equilibrium conditions, slow exchange; (d) equilibrated, slow exchange.

disproportionate invertomer populations were not obtained under equilibrium conditions. Protonation of alkyl amines[129] is a very rapid, essentially diffusion controlled reaction ($\Delta G^{\ddagger}$~2-3 kcal which is significantly lower than $\Delta G^{\ddagger}$ for nitrogen inversion).[130] Hence protonation "traps" the equilibrium mixture of amines, in this case XVIIa and XVIIb. This is not the same as the equilibrium mixture of protonated XVII. If nitrogen inversion is possible subsequent to protonation, the original mixture will equilibrate to a mixture representative of the thermodynamic equilibirium XVIIa-H^+ $\rightleftharpoons$ XVIIb-H^+. In solvents like excess TFA/$CDCl_3$ or dry HCl/ether, proton exchange and hence nitrogen inversion is very slow. Equilibration under these conditions occurs very slowly. Conversely, in dilute HCl solution, equilibration occurs rapidly. One of the most critical factors is the method of combining the reagents. For example, addition of XVII to TFA/$CDCl_3$ affords a mixture of ammonium salts in the same ratio as the mixture of invertomers (free base) present in solution at the time of quenching (i.e., quenching by TFA/$CDCl_3$ is very rapid relative to nitrogen inversion).

The reason for obtaining the equilibrium constant for XVIIa-H^+ $\rightleftharpoons$ XVIIb-H^+, was to provide a model for steric effects in our system. The relative size of $-CH_3$ and -H (or the relative amount of Van der Waals repulsion between $-CH_3$ and -H and the exo protons) is the principal modifier of Keq (XVII-H^+). This is in contrast to the duel factors influencing the equilibrium position of the free base. For the equilibrium XVIIa $\rightleftharpoons$ XVIIb, ΔG°_{298} = -1.47 kcal/mole (obtained from nmr of XVII in TFA/$CDCl_3$). The free energy difference can be considered to be composed of two parts: ΔG°_{E} which is defined as the free energy difference due to bishomoantiaromatic de-

destabilization of XVIIa relative to XVIIb, and ΔG°_{s} which is defined as the free energy difference due to destabilization of XVIIa resulting from Van der Waals repulsion of the $-CH_3$ by the exo protons. Van der Waal's repulsion between the exo protons and the lone pair electrons in XVIIb, $(\Delta G^{\circ}_{s'})$, constitute a destabilization of XVIIb relative to XVIIa. The terms $\Delta G^{\circ}_{s'}$ is opposite in effect of ΔG°_{s} and therefore should be opposite in sign. The combined terms $\Delta G^{\circ}_{s} - \Delta G^{\circ}_{s'}$ constitutes the free energy difference due to conformational rivalry between $-CH_3$ and lone pair electrons.

The model system examined to determine the steric contribution to ΔG°_{Total} (XVIIa $\rightleftharpoons$ XVIIb) is the free energy difference between XVIIa-H^+ and XVIIb-H^+. An important distinction between the two is that conformational rivalry in the latter is between $-CH_3$ and -H) rather than $-CH_3$ and lone pair as in the former. To interrelate the two steric free energy differences, data such as the free energy difference due to conformational rivalry between -H and lone pair is needed but unavailable in this system (the low temperature nmr spectrum of 7-azanorbornene might have provided some information. Alas, the spectrum (100 MHz) was unchanged to 203°). Nevertheless, an approximate value of ΔG° (H vs lone pair) can be obtained by use of ΔG° (LVa $\rightleftharpoons$ LVb).[133]



LVa LVb

$\Delta G^{\circ} = -0.3 \pm 0.2$ kcal/mole

although considerable controvery has existed in the past over both the sign and magnitude of ΔG° (LVa $\rightleftharpoons$ LVb),[122,134-141] the most recent

results from several groups generally agree within ± 0.2 kcal/mole[123,124,142-145] for ΔG° (LVa $\rightleftharpoons$ LVb) = -0.3 kcal/mole. Working backward, we first relate the two steric conformational energy differences:

ΔG_s° (Me-vs-lone pair) = ΔG_s° (Me vs H) - ΔG° (H vs lone pair)

or

ΔG_s° (XVIIa $\rightleftharpoons$ XVIIb) = ΔG° (XVIIaH$^+$ $\rightleftharpoons$ XVIIbH$^+$) - ΔG° (LVa $\rightleftharpoons$ LVb)

ΔG_s° (XVIIa $\rightleftharpoons$ XVIIb) = -0.57 + 0.3 kcal/mole

ΔG_s° (XVIIa $\rightleftharpoons$ XVIIb) = -0.27 kcal/mole

Now if we subtract the steric effect from ΔG°_{Total} (XVIIa $\rightleftharpoons$ XVIIb) we obtain the free energy difference due to bishomoantiaromatic interaction

$$\Delta G_E^\circ = \Delta G_T^\circ - \Delta G_s^\circ$$

$$\Delta G_E^\circ = -1.47 - (-0.37)$$

$$\Delta G_E^\circ = 1.2 \text{ kcal/mole}$$

One kcal/mole destabilization energy due to bishomoantiaromaticity seems small when compared to the destabilization energy due to antiaromaticity. For example, Breslow's electrochemical results[31] suggested 10-15 kcal/mole destabilization of cyclopropenyl carbanion systems. Nevertheless, 1 kcal/mole free energy difference between two states corresponds to an equilibrium constant of 5.67. This is significantly greater than the equilibrium constant for XXVIII $\rightleftharpoons$ XXVII, which was suggested to be due to purely steric effects.[36]

Data obtained on N-methyl-7-azanorbornene gave qualitatively the same results. Examination of the 100 MHz nmr spectra of XVI shows the effects of coalescence broadening on the olefinic proton resonance at 308°. Lowering the temperature only 15° reaches the coalescence temperature. Further cooling to 253° allows observation of two sharp triplets (Figure 33).

The major invertomer, XVIb, represents only 86% of the mixture, corresponding to a free energy difference of ΔG° = -0.913 kcal/mol. The smaller free energy difference in XVI, relative to XVII, is not easily understood. Probably subtle changes in the geometry on shortening the C_2-C_3 bond are responsible. One effect of shortening this bond is a decrease in angle, C_1-N-C_4, which is certainly reflected in the higher coalescence temperature and hence larger inversion activation energy. The differing coalescence temperatures of the olefinic and bridgehead protons allows calculation of $\Delta G^{\ddagger}$ at two temperatures. This in turn permits calculation of the enthalapy and entropy of activation. The temperature dependent parameters for the aforementioned calculations are listed below.

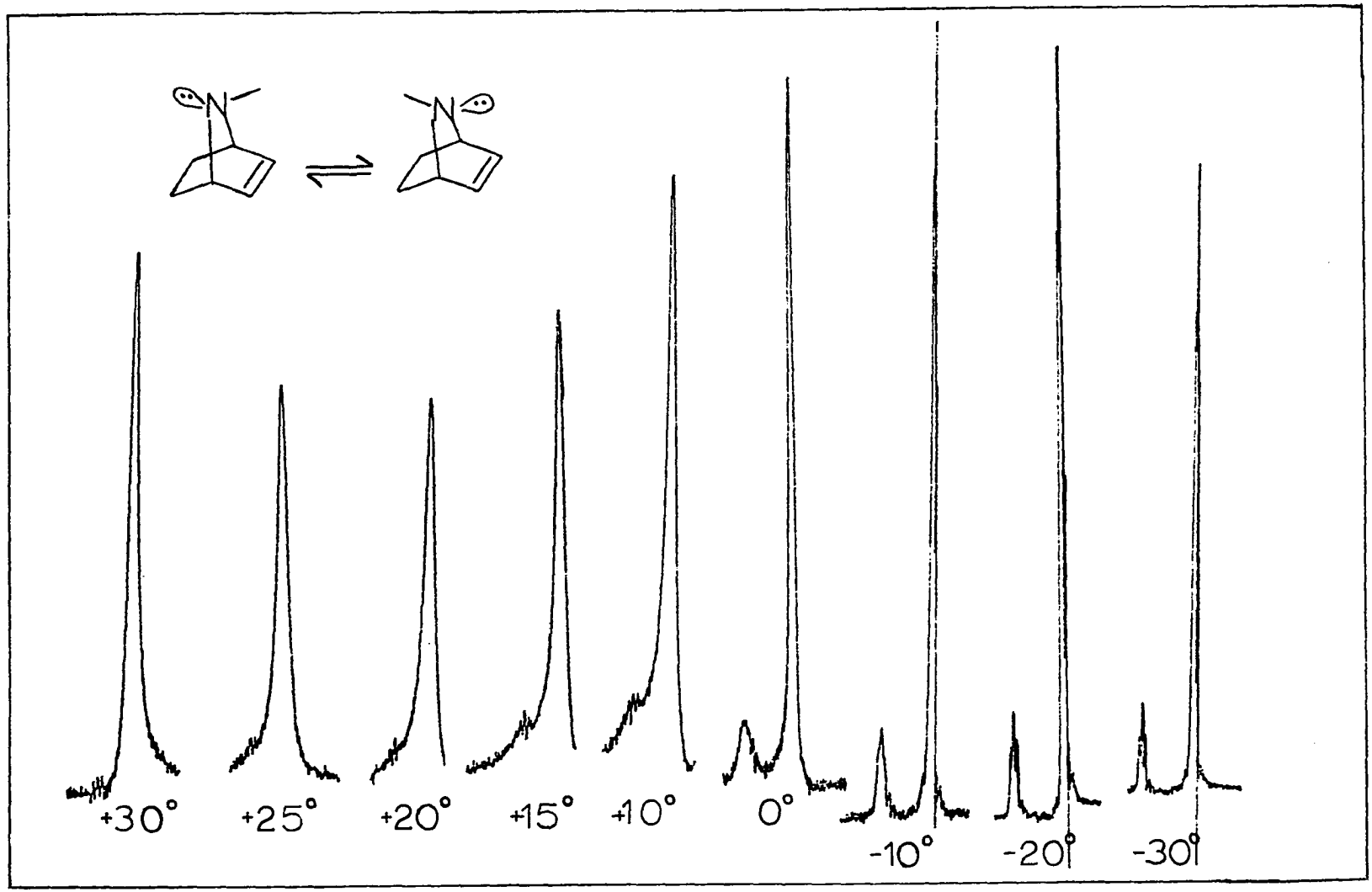
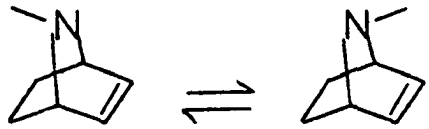


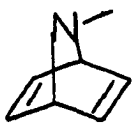
Figure 33. Partial 100 MHz nmr spectra of olefinic protons at various temperatures



	olefinic	bridgehead
Coalescence temperature	295	263
$\Delta\nu$	26 Hz	10 Hz
rate constant, k_c	58 sec^{-1}	22 sec^{-1}
activation energy, $\Delta G^{\ddagger}$	14.9 kcal/mole	13.7 kcal/mole

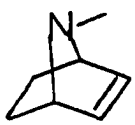
When the activation energy $\Delta G^{\ddagger}$ is known at two temperatures, substitution into the equation relating free energy, enthalapy, and entropy gives two equations and two unknowns. Simultaneous soltuion of the two equations, ($\Delta G_T^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) yields the values $\Delta H^{\ddagger} = 14.3$ and $\Delta S^{\ddagger} = -0.0022$. Although these values were calculated from approximate rate constants, they appear reasonable. The very small entropy of activation ($\Delta S^{\ddagger} = 0$ within experimental error) is consistent with the theoretical value of 0. (for nitrogen inversion, the transition state has the same number of symmetry elements as the reactant's number of symmetry elements; hence, theoretical entropy difference is R ln (# in Transition state/# in reactant) = R ln 1 = 0

The activation energies obtained for XVI appear somewhat large when compared to the activation energy of LVI [146] and LVII[147,148]



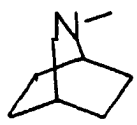
LVI

14.9



XVI

14.9

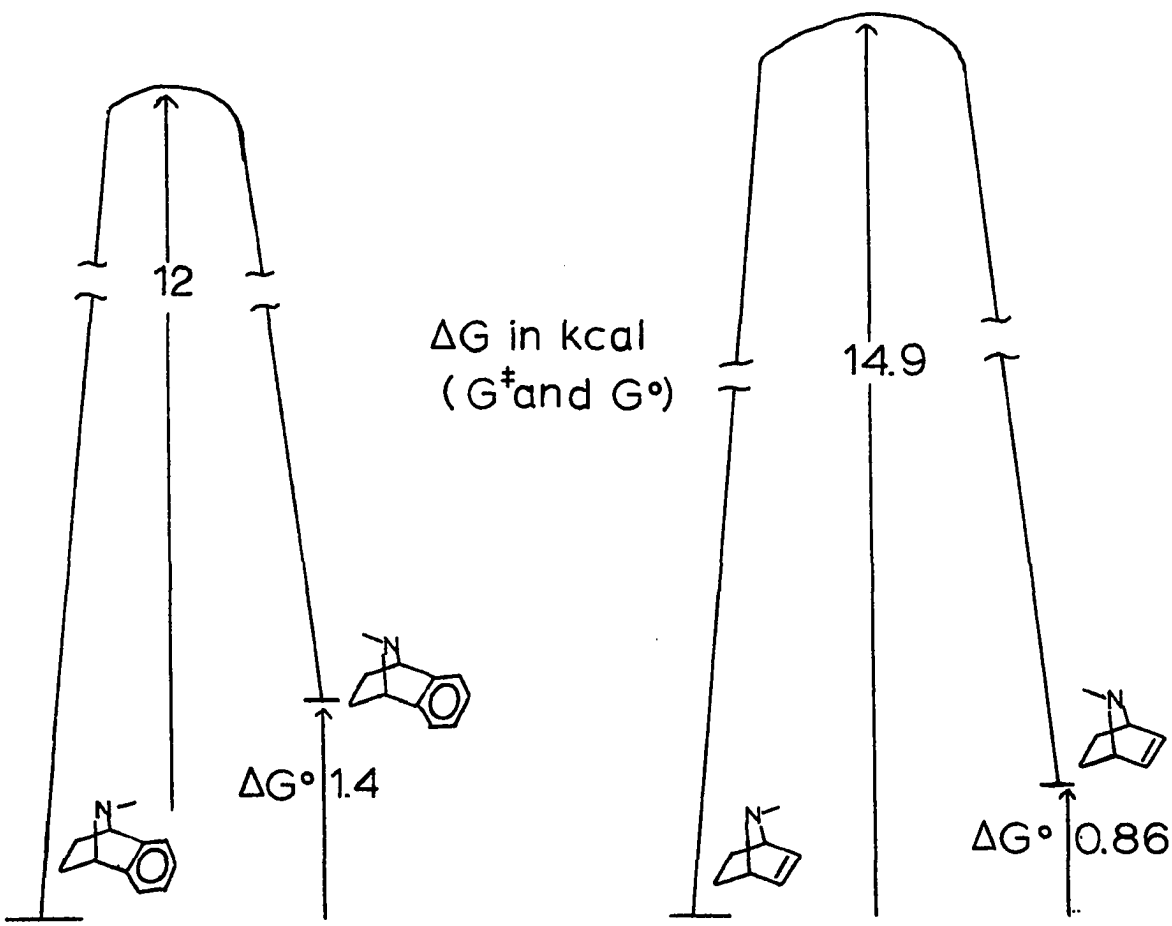


LVII

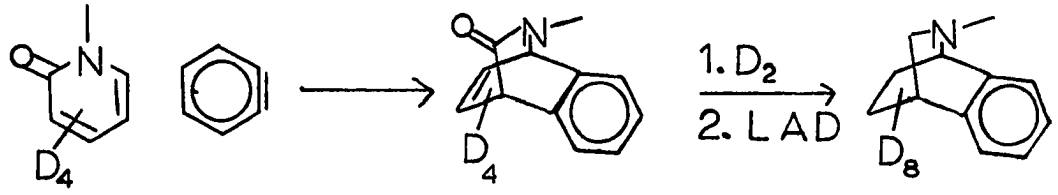
11 kcal

The actual value of the activation energy is probably between 11 and 15 kcal/mol, or very near that of XVII.

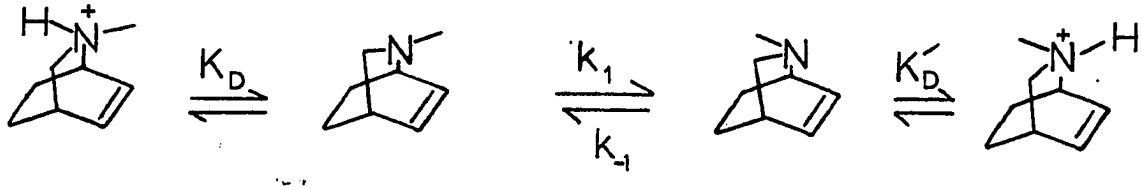
A simple summarization of the data obtained for XVI and XVII is seen in the energy versus reaction plots.



Attempted dynamic nmr experiments with N-methyl-8-azabicyclo-[2.2.2]octene, XVIII, and N-methyl-8-azabenzobicyclo[2.2.2]octene, XIX, afforded disappointing results. Several 100 MHz nmr spectra for XVIII and XIX were obtained from 308° to 136°. Compound XIX was examined at 300 MHz from 308° to 223°. No evidence of coalescence could be observed in either case. The complexity of the spectra was greatly simplified, at least for XIX, by preparation of XIX-d_8, by the method outlined below.



The spectrum of XIX-d_8 shows only the N-CH_3 singlet, in addition to the aromatic proton resonance). (See Figure 34) Examination of the 100 MHz nmr spectra of XIX-d_8 from +35 to -137° still showed no change whatsoever. We then made an attempt to obtain information on the inversion equilibra employing pH dependent nmr.[150,151] This technique relies on the fact that interconversion of a pair of protonated amines requires the intermediacy of the free base:



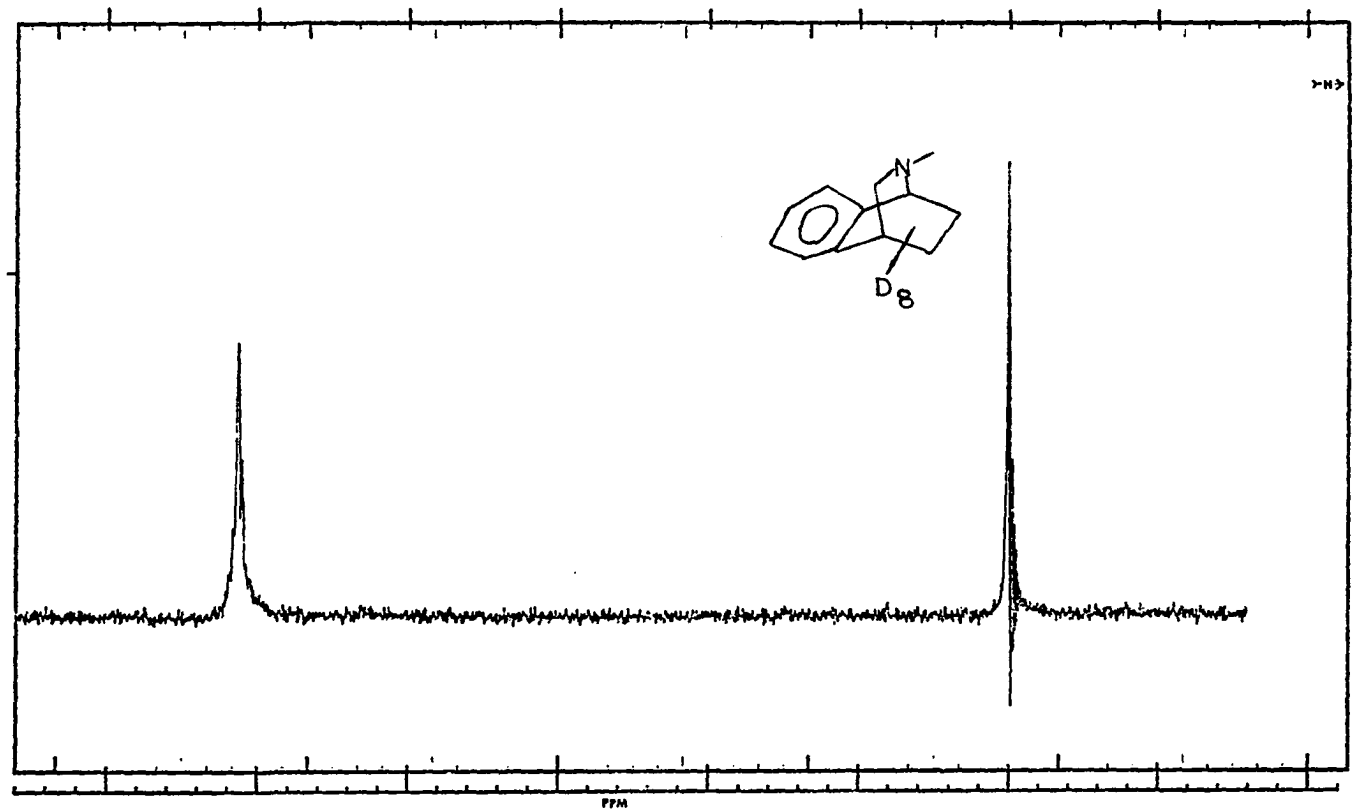


Figure 34. 60 MHz nmr spectrum of XIX-d_8, $CDCl_3$

where: K_D and K_D' are acid dissociation constants

k_1 and $\underset{-}{k}_1$ are forward and reverse rate constants for nitrogen inversion

The overall reaction rate can be obtained by measuring the amount of line broadening ($\Delta W\frac{1}{2}$) as a function of pH (line broadening occurs when the proton exchange rate is of the same order of magnitude as the frequency difference of the exchangine sites (Figure 35). When $K_D = K_D'$, the slope of the line obtained by plotting $\Delta W\frac{1}{2}$ vs. 1/pH is proportional to the rate constant k_1 (or k_2). The ratio of slopes k_1 and k_2 is equal to the equilibrium constant. This apparently is not valid when $K_D \neq K_D'$. Implicit in the equality $K_D = K_D'$ is the fact K_{eq} (free base) equals K_{eq} (protonated amine). This is not true for the amines we examined (XVII through XIX). Nevertheless we prepared plots of line broadening versus 1/pH (Figure 36) and found that the ratio of slopes was not equal to K_{eq}. Failure of both temperature and pH dependent nmr methods restricted the amount of information obtainable for compounds XVIII and XIX. The equilibrium constants were obtained from the nmr spectra of XVIII and XIX in trifluoroacetic acid solution. For example, Figure 37 shows the nmr spectrum of XIX in 20% TFA/$CDCl_3$. Because protonation is fast with respect to nitrogen inversion, the ratios of the two protonated invertomers observed in Figure 37 is the same as the ratio of the two invertomers present in the free base. Hence, this ratio corresponds to the equilibrium constant for nitrogen inversion (XIXa $\rightleftharpoons$ XIXb, Table V). From Figure 37 we see the N-methyl resonance of the major component of the mixture as upfield of the minor component. In bicyclo(2.2.2)octenes, (see Table I) the methyl group upfield is <u>syn</u> to the π-system. Assuming the net anisotropy

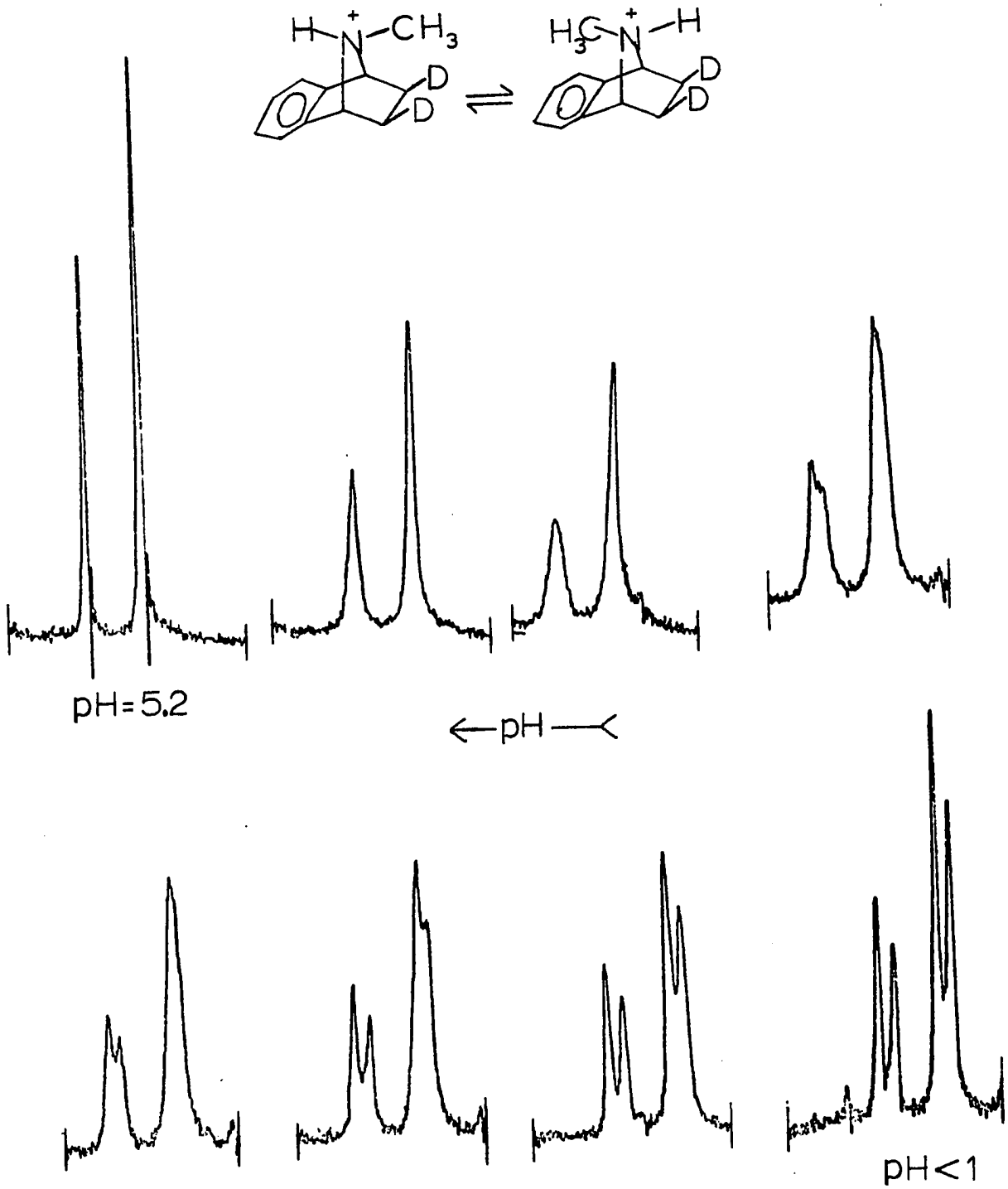
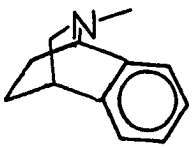


Figure 35. Partial 60 MHz nmr spectra (N-methyl resonance) as a function of the pH

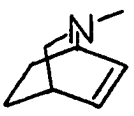
Table V



XIX b

K = 32

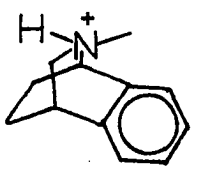
$-\Delta G^\circ$ = 2.04 kcal/mole



XVIII b

K = 19

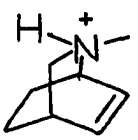
$-\Delta G^\circ$ = 1.75 kcal/mole



XIX b-H$^+$

K = 3

$-\Delta G^\circ$ = 0.65 kcal/mole



XVIII b-H$^+$

K = 3

$-\Delta G^\circ$ = 0.65 kcal/mole

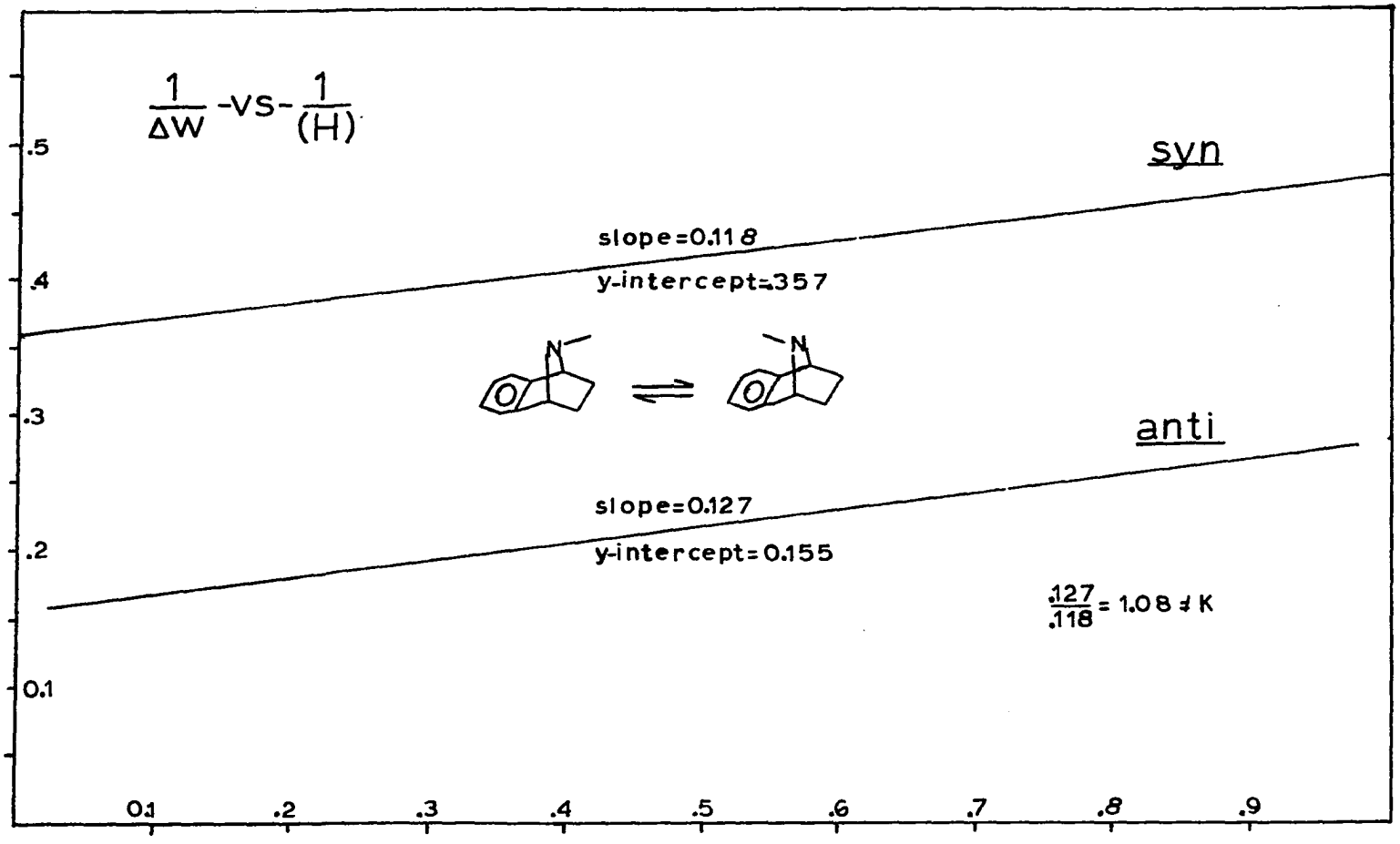


Figure 36. Plot of line broadening (N-methyl resonance) versus 1/[H]

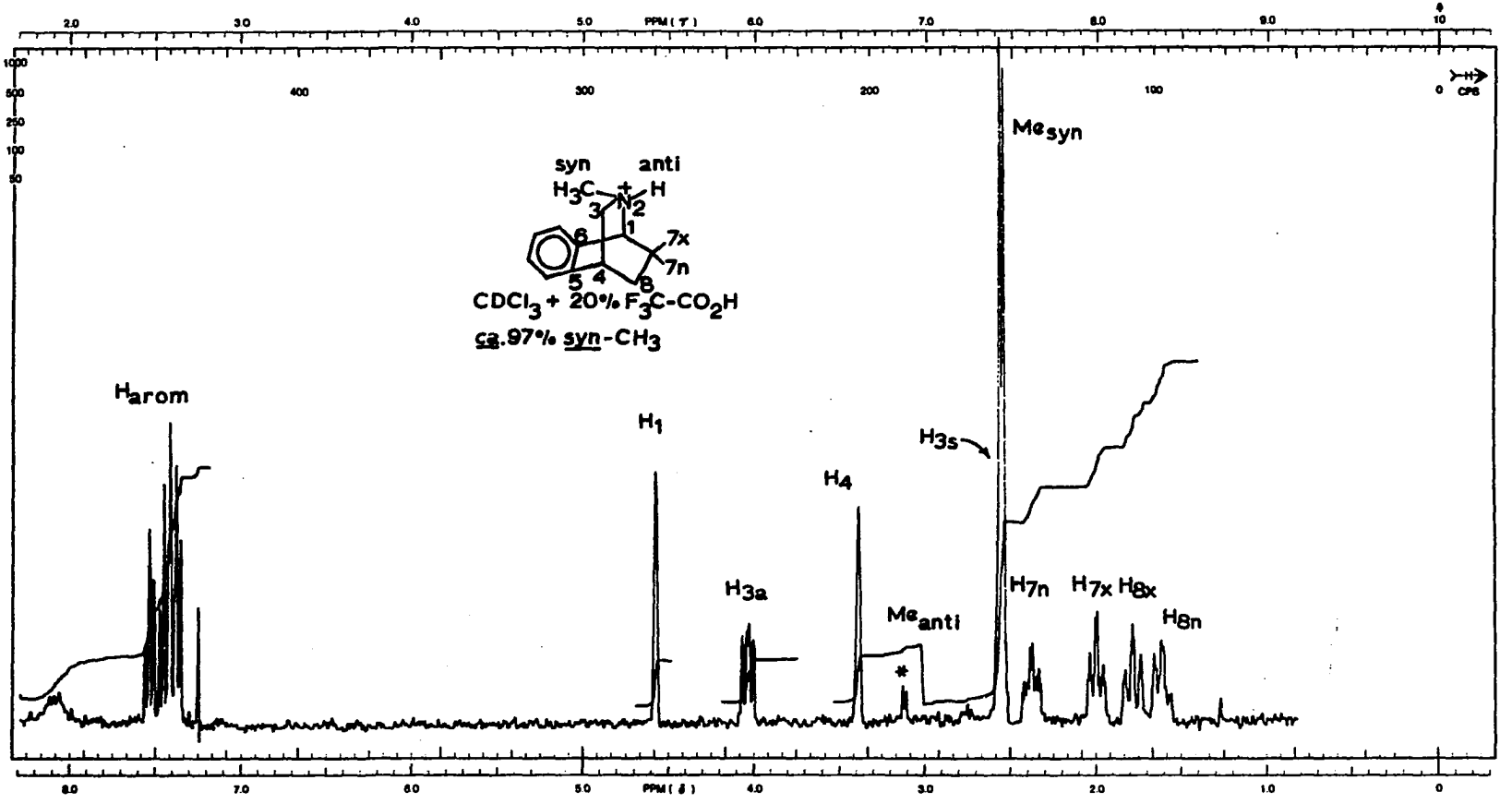


Figure 37. 300 MHz nmr spectrum of XIX-H^+, 80% $CDCl_3$: 20% CF_3CO_2H

effects are the same in our azabicyclo[2.2.2]octenes and the corresponding carbocyclic analogues, XIXa is the minor invertomer (Table V), contrary to our predictions based solely upon consideration of electronic effects. To obtain the true equilibrium constant for ($XIXaH^+ \rightleftharpoons XIXbH^+$), the nmr spectra were recorded under conditions which allow equilibration (Table V). This was accomplished by addition of less than one equivalent trifluoroacetic acid (TFA) to the amine. Ten minutes later enough TFA and $CDCl_3$ was added to make a 20% TFA in $CDCl_3$ solution. The excess base present during the ten minute period catalyzes proton exchange and hence, equilibration.

Assuming the a priori nmr assignment are correct, it appears that in the azabicyclo[2.2.2]octenes steric effects completely dominate the direction of nitrogen inversion equilibrium. The effect of homoallylic resonance is vanishingly small with respect to the effect of Ven der Waals repulsion between the exo protons and the N-methyl moiety.

Conditions of slow exchange in the nmr spectra of XVIII and XIX could not be attained. Nevertheless, the equilibrium constants for XVIII and XIX were obtained by examination of the nmr specta in trifluoroacetic acid. By varying the method of nmr sample preparation, equilibrium constants representative of the free base and its conjugate acid were obtained (Table V). In the azabicyclo[2.2.2]octenes, the prodominant invertomer was XVIIIb (XIXb), contrary to our predictions. The results indicate that steric effects (Van der Waal's repulsion of $N-CH_3$ by the exo hydrogens) completely dominate the equilibrium position in XVIIIa $\rightleftharpoons$ XVIIIb and XIXa $\rightleftharpoons$ XIXb relative to any stabilization to be gained from homoallylic conjugation.

Summary

In this section we have suggested model systems which we hoped would allow observation of the destabilizing effects of bishomoantiaromaticity, relative to the stabilizing effects of homoallylic conjugation. Accordingly, compounds XVI-XIX were prepared by straightforward methods involving an initial Diels-Alder reaction (also prepared was the previously unknown 7-azabicyclo(2.2.1)hept-2-ene, XLIX).

Both kinetic and thermodynamic properties of XVI and XVII were obtained via temperature dependent nmr experiments. Results obtained for these two compounds were in agreement with out predictions, assuming our nmr assignments are correct. The results indicated that XVIa and XVIIa (Table IV) were the minor components of their respective mixtures. This we suggested was due to bishomoantiaromatic destabilization of XVIa (XVIIa). We subsequently found that steric effects also contribute to the observed confromational bias. To separate the steric and electronic factors, an approximate numerical method was employed. The results of this treatment suggest ca. 1 kcal/mole destabilization due to bishomoantiaromaticity.

Experimental

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-8 infrared spectrometer. Mass spectra were obtained on a Hitachi-Perkin Elmer RMU-7E mass spectrometer operated at 70 eV. For compounds XLVII, XLVIII, XLIX, and XVI, the filament chamber was cooled to room temperature. Professor Marc Anteunius, Laboratorium voor Organishche Chemie, Rijksuniversiteit Gent (Belgium) provided 300 MHz nmr spectra. The 60 and 100 MHz nmr spectra were obtained on Varian T-60 and XL-100 spectrometers, respectively. Gas chromatography work was done on a Varian 90-P gas chromatograph.

Attempted Acyloin Condensation of N-Methyl or N-Benzyl-Cis-2,5-Dicarboethoxy-Pyrrolidine[152]

Method (A)

Sodium (6 g, 0.26 moles) was cut in small cubes and added to dry toluene (300 ml). This was heated to reflux with rapid stirring until the sodium was finely dispersed. While maintaining the temperature at 80-85°, the diester (5 g, 0.22 moles) and $ClSi(CH_3)_3$ (15 ml) were added simultaneously through separate dropping funnels. After 3 hrs the reaction was quenched with cautious addition of dilute hydrochloric acid. The aqueous layer was made basic with sodium carbonate then extracted with ether (500 ml). Only black polymeric tar was obtained on removal of solvent.

Method (B)

In 250 ml, toluene under N_2, sodium (1.5 g, 0.065 moles) and potassium (7.5 g) were heated until the molten alloy formed. The flask was cooled to 0° whereupon the diester (3 g, 0.013 moles) and $ClSi(CH_3)_3$ (10 ml) were added over a ten-minute period. During addition the color of the solution went from light green to black. Workup as above again yielded only black tarry material.

Method (C)

Nitrogen gas was bubbled through a solution of naphthalene (27 g, 0.21 moles) in dry THF (500 ml) for ten minutes. With rapid stirring, sodium (4.6 g, 0.2 moles) was added rapidly to the solution. To this resulting dark green solution, diester (6.25 g, 0.02 moles) was added. Within ten minutes the solution turned dark brown. Then, on addition of $ClSi(CH_3)_3$ (10 ml) the solution slowly turned light orange. Workup as above indicated none of the desired product.

Method (D)

In a flask fitted with N_2 line, dry ice condenser and dropping funnel was placed anhydrous ammonia (150 ml) and sodium (0.97 g, 0.042 moles). An ether solution (15 ml) of diester (2.4 g, 0.01 moles) was added to the refluxing ammonia. Within one hour tlc indicated the abcence of starting material. Ether (50 ml) was added and the condenser removed, allowing the ammonia to evaporate. Quenching with dilute hydrochloric acid, neutralization with sodium carbonate , and separation of the ether yielded only traces of organic material. Continuous liquid-liquid extraction of the aqueous phase with ether likewise yielded only traces of organic material, none of which was the desired acyloin.

N-Benzylpyrrole

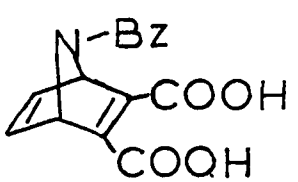
Method (A)

The method of Tuite and Snyder[153] was employed: 2,5-Dimethoxy-tetrahydrofuran (66 g, 0.5 moles) plus benzyl amine (54 g, 0.5 moles) were added to glacial acetic acid (100 ml) and heated to reflux. After one hour the acetic acid was removed by distillation at 25 torr. (aspirator vacuum) Distillation of the remainder afforded a 51% yield of N-benzylpyrrole (40.1 g) b.p. 66-68° (0.35 torr).

Method (B)

This preparation is similar to but simpler than that of C. F. Hobbs et al.[154] A total of 25 g NaH (1.1 mole) in 5 g portions was added to DMSO (300 ml), forming a gray dispersion. Addition of pyrrole (67 g, 1.0 mole) required 1.5 hours. Subsequent additon of benzyl chloride (127 g, 1 mole) over a 3 hour period was exothermic (the distinct odor of benzyl pyrrole was apparent almost immediately). This mixture was stirred for an additional 2 hours at room temperature, then diluted with an equal volume of H_2O. This was extracted with ether (3 x 400 ml), which was back extracted with H_2O (500 ml). The organic phase was dried over sodium sulfate followed by removal of solvent on a rotary evaporator. Distillation at 66°-69° (0.35) torr afforded 119 g N-benzyl pyrrole (75% yield).

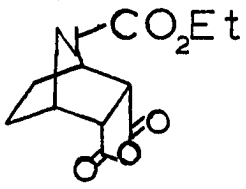
N-Benzyl-7-Azabicyclo(2.2.1)hepta-2,5-diene-2,3-Dicarboxylic Acid (XL)



The method of Shafi'ee& Hite[80] was employed. Rapid addition of N-benzyl pyrrole (75 g, 0.48 moles) to acetylenedicarboxylic acid[155] (54.5 g. 0.48 moles) in refluxing ether (500 ml) turned

the colorless solution to yellow within one hour. After 24 hours the solution (orange) was filtered. The filtrate was returned to the reaction flask and refluxed for an additional 5 days, then refiltered. The combined precipitates were washed repeatedly with hot acetone until a colorless product was obtained (23 g, 18% yield) m.p. 210-212° (lit. 210-212°[155,156]). Elevation of the melting point (to 211-213°) is accomplished by recrystallization from boiling water; however, this was not necessary for our purposes (and recrystallization lowered the overall yield).

N-Carboethoxy-7-Azabicyclo(2.2.1)heptane-2,3-endo-Dicarboxylic Acid Anhydride (XLIV).



Compound XL (10 g, 36.9 mmoles) was dissolved in 10% aqueous sodium carbonate (100 ml). The resulting solution was hydrogenated over 10% palladium on charcoal at 45 pounds H_2 pressure. After absorption of 3 equivalents of hydrogen, the catalyst was removed by filtration. To the filtrate containing the hydrogenation product was added excess ethyl chloroformate, and the resulting solution was stirred overnight at room temperature. The solution was then acidified with hydrochloric acid and extracted with chloroform (3 x 75 ml). The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated, affording XLIII as an odorless syrup (8.2 g, 86%). This diacid was characterized as the anhydride, XLIV, which could be obtained *via* sublimation of syrupy XLIII at 110° (0.1 torr). This procedure afforded XLIV (5.8 g, 76%), which recrystallized from ether-hexane to afford colorless crystals, mp 111.5-112.8°.

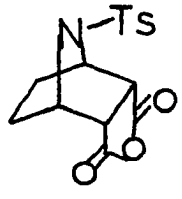
60 MHz nmr, ($CDCl_3$): δ 1.30 (triplet, J=6 Hz, 3H, $-OCH_2\underline{CH}_3$), δ 1.61-2.1 (complex multiplet, 4H, 5,6-exo and endo ring protons), δ 3.73 (multiplet, 2H, 2,3-exo ring protons), δ 4.15 (quartet, J=6 Hz, 2H, $-OC\underline{H}_2CH_3$), δ 4.70 (multiplet, 2H, 1,4-(bridgehead) protons) see figure 5.

70 eV mass spectrum: m/e 239 (molecular ion), 141 (base peak), 140, 139, 122, 68. (see figure 6)

IR (KBr pellet), cm^{-1}: 2980 (w, C-H), 1860 and 1785 (s, C=O strech of cyclic anhydride), 1690 (s, C=O strech of carbamate), 900 (s, C-O strech of cyclic anhydride).

Analysis for $C_{11}H_{13}NO_5$: Calculated C 55.23, H 5.48, Found, C 55.30, H 5.35.

N-Toluenesulfonyl-7-Azabicyclo(2.2.1)heptane-2,3-endo-Dicarboxylic Acid Anhydride (XLVI).



This was prepared in the same fashion as was XLIV. Hydrogenation-hydrogenolyis of XL (10 g, 36.9 mmoles) followed by treatment of the resulting solution with excess p-toluenesulfonyl chloride and workup as above affords XLV (12.0 g, 95.9%) as a gummy material.

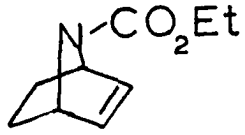
60 MHz nmr, C_5D_5N: δ 1.53-2.50 (multiplet, 4H, 5,6-exo and endo ring protons), δ 2.3 (singlet, 3H, $ArC\underline{H}_3$), δ 3.90 (multiplet, 2H, 2,3-exo ring protons), δ 4.70 (multiplet, 2H, 1,4-(bridgehead) protons), δ 5.50 (singlet, 2H $-CO_2\underline{H}$), δ 7.63 (AB quartet, 4H, J_{AB}=8 Hz, aryl ring protons) see figure 7. The diacid is easily converted to the corresponding anhydride (XLVI) by sublimation at 150° (0.05 torr) yield 10.0 g, 84.4%. Recrystallization from acetone affords small colorless crystals, mp 230-232°.

IR (KBr pellet), cm^{-1}: 3070 (ω, =C-H), 2980 (ω, C-H), 1865 and 1785 (s, C=O of anhydride), 1375 and 1140 (sh, S-O) 1590 (ω, C=C), 905 of anhydride).

70 eV mass spectrum: m/e 321 (molecular ion), 223, 166, 155, 122, 91, 68 (base peak) see figure 8.

Analysis for $C_{15}H_{15}NO_5S$: Calculated, C 56.06, H 4.70; Found, C 56.16, H 4.92.

N-Carboethoxy-7-Azabicyclo(2.2.1)hept-2-ene (XLVII).



Compound XLIII (5.0 g, 19.5 mmoles) was dissolved in an electrolysis solution which consisted of water (20 ml) triethylamine (2.5 ml) and pyridine (175 ml). A direct current (80 v, initial current 350 ma, Pt wire electrodes) was passed through this solution for 15 hr while the solution was maintained at 20° via external cooling. At the conclusion of the electrolysis, the current had dropped to 40 mamps. The solution was then quenched with dilute aqueous hydrochloric acid, and the resulting solution was extracted with diethyl ether (500 ml). The ether layer was then extracted with 10% aqueous sodium hydroxide solution to recover 0.6 g XLIII. The ether layer was dried (Na_2SO_4), filtered, and then concentrated to afford a brown oil. A short column chromatography on neutral alumina with hexane eluent gave 749 mg (25.4% based on unrecovered starting material) XLIII as a colorless very sweet smelling oil. (During the column chromatography, XLVIII was detectable by odor at concentrations lower than were detectable by thin layer chromatography with iodine development. However, when XLVIII was neat, or in very concentrated solutions, no odor was detectable.) An

analytical sample was prepared via preparative gc (0.64 cm by 3m column of 20% FFAP on Chromasorb W, all gc components-injector, detector, and column $\leq$ 140°.

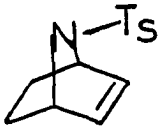
60 MHz nmr ($CDCl_3$): δ 1.26 (triplet, J=6 Hz, 3H, $-OCH_2\underline{CH_3}$), δ 1.13 (double doublet, $J_{5_n\,5_x}$ = 9-10 Hz, and $J_{5_n\,6_x}$ = 3-4 Hz, 5,6-endo ring protons), δ 1.90 (multiplet, 2H, 5,6-exo ring protons), δ 4.07 (quartet, J=6 Hz, 2H, $-O\underline{CH_2}CH_3$), δ 4.74 (multiplet, 2H, 1,4-(bridgehead) protons), δ 6.24 (unsymmetrical triplet, 2H, 2,3-(olefinic)protons). see figure 9

70 eV mass spectrum: m/e 167 (molecular ion), 139, 94, 80, 66, 41, 39 (base peak). see figure 10

IR (film), cm^{-1}: 3020 (w,=C-H), 2995 (w, C-H), 1710 (s, br, C=O), 1270 (m, C-N), 690 (m, cis double bond). For analysis, XLVII was sealed in a capillary under vacuum after gc seperation and subsequent microdistillation.

Analysis for $C_9H_{13}NO_2$; C 64.65, H 7.84; Found C 64.88, H 7.87.

N-Toluenesulfonyl-7-Azabicyclo(2.2.1)hept-2-ene (XLVIII).



Preparation of XLVIII was similar to XLVII; i.e., XLV (2.3 g, 6.78 mmoles) was dissolved in the electrolysis solution (100 ml) and subjected to an initial current of 160 mamps between platinum wire mesh electrodes (ca. 50 volts). When the current dropped below 50 mamps (12 hours) the electrolysis was terminated, and the solution made acidic with hydrochloric acid. This was extracted with two volumes chloroform. The organic layer was washed with one volume saturated sodium bicarbonate followed by one volume water, then dried over sodium

sulfate. Removal of solvent gave a heavy black oil which was chromatographed on neutral alumina. Elution with hexane afforded XLVIII as a crystalline solid on concentration of the hexane solution. Recrystallization from hexane gave 205 mg m.p. 91-92° (0.82 mmoles, 12%).

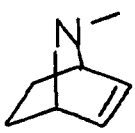
60 MHz nmr, ($CDCl_3$): δ 1.07 (double doublet, $J_{5_n 5_x}$ = 11-12 Hz $J_{5_n 6_x}$ = 3-4 Hz, 2H, 5,6-endo ring protons), δ 2.03 (multiplet, 2H, 5,6-exo ring protons), δ 2.42 (singlet, 3H, Ar-CH_3), δ 4.64 (multiplet, 2H, 1,4-(bridgehead) protons), δ 5.73 (asymmetric triplet, 2H, 2,3-(olefinic)-protons), δ 7.41 (AB quartet, J=8 Hz, 4H, aryl ring protons). see figure 11

70 eV mass spectrum: 249 (moleuclar ion), 221, 155, 106, 91 (base peak). see figure 12

IR (KBr pellet), cm^{-1}: 3090 (w, =C-J), 2995 and 2960 (w, C-H), 1590 (w, C=C), 1335 and 1150 (s, S-O), 690 (s, cis double bond).

Analysis for $C_{13}H_{15}NSO_2$: Calculated, C 62.62, H 6.06; Found, C 62.50, H 5.99.

N-Methyl-7-Azabicyclo(2.2.1)hept-2-ene (XVI)



N-Carboethoxy-7-azabicyclo(2.2.1)hept-2-ene (XLVII, 749 mg, 4.49 mmoles) was dissolved in benzene (30 ml). To the resulting solution was added a benzene solution (23 ml) of diisobutylaluminum hydride (0.61 meq/ml). After stirring for 4 hours at room temperature, an additional 5 ml DIBAL-H solution was added (total 28 ml, 17.1 mmoles). After 4 more hours the reaction mixture was cooled to 0° and quenched with excess methanol. (If the mixture is not cooled to 0° before quenching, an unfilterable gel is obtained. In this case

the product can be obtained by addition of concentrated potassium hydroxide and extraction with several volumes of chloroform. The reaction mixture was filtered from the precipitated salts ($Al(OMe)_3$) and combined with an equal volume of a saturated solution of picric acid in 95% ethanol, whereupon yellow crystals of XVI-picrate precipitated immediately. Recrystallization from 95% ethanol afforded the pure picrate (1300 mg, 86%) as yellow needles, m.p. 225 (decomposition).

Analysis for $C_{13}H_{14}N_4O_7$; C 46.16, H 4.17; Found C 45.93, H 3.98.

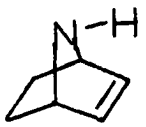
The free base was obtained by treating the picrate with concentrated aqueous potassium hydroxide followed by extraction with chloroform or steam distillation followed by ether extraction. XVI was isolated by preparative gas chromatography on a 0.64 cm by 1.5 m column (28% Pennwalt 223 on 80/100 Gas-Chrom R-4% KOH). All gc components (injector, column, detector) were maintained at or below 100-110°, nitrogen carrier gas.

60 MHz nmr ($CDCl_3$): δ 0.96 (double doublet, 2H, $J_{5_n5_x}$ = 11-12 Hz, $J_{5_n6_x}$ = 3-4 Hz, 5,6-endo protons), δ 1.75 (multiplet, 2H, 5,6-exo protons), δ 2.04 (singlet, 3H, N-CH_3), δ 3.69 (multiplet, 2H, 1,4-(bridgehead) protons), δ 5.98 (broad singlet, 2H, 2,3-(olefinic) protons). see figure 15

70 eV mass spectrum: m/e 109 (molecular ion), 94, 81, 80, 66, 53, 42, 39 (base peak). see figure 16

IR (film), cm^{-1}: 3080 (w, =C-H), 2960 (w, C-H), 690 (m, cis double bond).

Azabicyclo(2.2.1)hept-2-ene (XLIX)



Compound XLVIII (204 mg, 0.82 mmoles) was dissolved in a mixture of liquid ammonia (20 ml) and ether (10 ml). Small clean portions of sodium were added until the blue color persisted for one minute. Ammonia was allowed to evaporate by removing the dry ice-acetone condenser, leaving an ether solution. This was extracted with an equal volume of dilute hydrochloric acid. The aqueous phase was made strongly basic with potassium hydroxide, then extracted with $CHCl_3$ (10 ml). Evaporation of solvent with a stream of dry nitrogen at room temperature afforded 70 mg XLIX as a colorless liquid (0.73 mmoles, 89%).

60 MHz nmr ($CDCl_3$): δ 1.02 (double doublet, 2H, $J_{5_n,5_x}$ = 11-12 Hz, $J_{5_n,6_x}$ = 3-4 Hz, 5,6-endo protons), δ 1.75 (multiplet, 2H, 5,6-exo protons), δ 1.76 (singlet, 1H, N-H protons, exchanged on addition of D_2O), δ 4.12 (multiplet, 2H, 1,4-(bridgehead) protons), δ 6.23 (asymmetric triplet, 2H, 2,3-(olefinic) protons) see figure 13.

70 eV mass spectrum: m/e 95 (molecular ion), 94, 80, 67, 66, 51, 42, 39 (base peak), 28; see figure 15

IR (film), cm^{-1}: 3250 (br, N-H), 3070 (w, =C-H), 2960 (s, C-H), 1650 (br, N-H), 1260 (m, C-N), 790 (s, N-H).

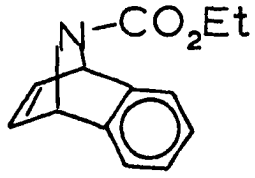
Addition of a saturated solution of picric acid in 95% ethanol precipitated XLIX-picrate immediately. Recrystallization from 95% ethanol afforded yellow needles, mp 208-210° (decomposition).

Analysis for $C_{12}H_{12}N_4O_7$: Calculated, C 44.45, H 3.73, N 17.28; Found, C 44.21, H 3.85, N 17.30.

N-Carboethoxypyrrole

The title compound was prepared from pyrrylpotassium in tetrahydrofuran.[158] Thus, pyrrole (51 g, 0.76 moles) was added dropwise to a mixture of tetrahydrofuran and potassium (30 g, 0.75 moles) under one atomosphere nitrogen. To this was added ethyl chloroformate (80 g, 0.75 moles) over a one hour period (exothermic). The resultant mixture was quenched with water (10 ml) filtered, dried over magnesium sulfate, and concentrated. Distillation at atmospheric pressure (fraction collected, bp 180-182) afforded N-carboethoxypyrrole (54.2 g, 52%).

N-Carboethoxy-1,4-Dihydronaphthalen-1,4-imine (L)



N-carboethoxy pyrrole (7.9 g, 0.057 moles) was dissolved in dry THF (100 ml) and set to reflux. Equimolar amounts of isoamyl nitrite and anthranilic acid (in THF solution) were added simultaneously via separate dropping funnels. The total time for addition was 2-1/2 hours, which was followed by an additional 1-1/2 hours reflux. THF was removed from the crude reaction mixture by disillation, then replaced with an equal volume of chloroform. This was washed with equal volumes of water, saturated sodium bicarbonate and finally water. Drying over sodium sulfate and concentration left a black oil which was chromatographed on neutral alumina. (10% ethyl acetate/ hexane eluent). The product, L, (6.2 g, 51%) was recrystallized from ether/hexane to give colorless needles mp. 59.5-60.0°.

60 MHz nmr ($CDCl_3$): δ 1.07 (triplet, 3H, J=7 Hz, $-OCH_2\underline{CH}_3$), δ 3.95 (quartet, 2H, J=7 Hz, $O\underline{CH}_2CH_3$), δ 5.45 (asymmetric triplet, 2H, 1-4-(bridgehead) protons), δ 6.73 to 7.23 (complex mult. 6H, aromatic and

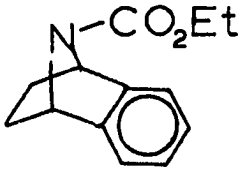
olefinic protons) see figure 17.

70 eV mass spectrum: m/e 216, 215 (molecular ion), 189, 170, 115, 65, 51. see figure 18

IR (KBr pellet) cm^{-1}: 3090 (sh, =C-H), 2290 (sh, C-H), 1690 (br, s, C=O), 1250 (s, C-N), 1100 (m, C-O), 760 (m, 1,2-disubstituted aromatic ring), 700 (sh, cis double bond).

Analysis for $C_{12}H_{13}NO_2$: Calculated C 72.54, H 6.09, N, 6.51; found C 72.73, H 6.01, N 6.59.

N-Carboethyoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine-(L)



Compound L (1-g, 4.65 mmoles was dissolved in 50 ml ethyl acetate with a spatula tip of 5% Pd/C. This was hydrogenated under 3 atmospheres H_2 for one hour. Filtration of catalyst and solvent removal leaves a colorless oil. Microdistillation (60°, 0.1 torr) afforded LI (0.93 g, 92%) as a colorless oil. Purification for analysis was accomplished via gas chromatography (0.64 cm by 3m column, 20% FFAP on Chromasorb W, column temperature 170°).

60 MHz nmr ($CDCl_3$): δ 1.10 (triplet, 3H, J=7 Hz, $-OCH_2\underline{CH_3}$), δ 1.18 (multiplet, 2 H, 2,3-endo-protons), δ 2.08 (multiplet, 2H, 2,3-exo protons), δ 3.98 (quartet, 2H, J=7 Hz, $O\underline{CH_2}CH_3$), δ 5.12 (multiplet, 2H, 1,4-(bridghead) protons), δ 7.05 (multiplet, 4H, aromatic ring protons) see figure 19.

70 eV mass spectrum: m/e 217 (molecular ion), 189, 151, 130, 117, 116 (base peak), 91, 89, 77, 63, 51 see figure 20.

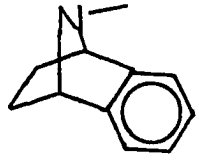
IR (film), cm^{-1}: 2980 (w, =C-H), 1715 (br, s, C=O), 1260 (m, C-N), 1100 (m, C-O), 745 (s, 1,2 disubstituted double bond).

Analysis for $C_{13}H_{15}NO_2$: Calculated C 71.87,H 6.96, found C 72.17, H 6.98.

N-Carboethoxy-1,2,3,4-Tetrahydronaphthalen-1,4-imine-2,3-exo,exo-d_2

The procedure for the preparation of LI was followed, substituting deuterium gas for hydrogen. Catalytic deuteration of L (5 g, 23 mmole) afforded on workup LI-d_2 (4.8 g, 96%).

N-methyl-1,2,3,4-tetrahydonaphthalen-1,4-imine (XVII)



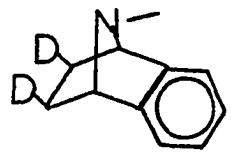
A solution of LI(5 g, 23 mmoles) in 20 ml dry tetrahydrofuran was added dropwise to a stirred solution of lithium aluminum hydride (0.91 g, 24 mmoles) in 30 ml dry THF. The mixture was heated to reflux for 8 hours. On cooling, the mixture was quenched with one ml water, one ml 10% sodium hydroxide, and 3 ml water. The precipitated aluminum salts were filtered from solution, and solvent removed affording crude XVII. Sublimation at 50° (0.1 torr) afforded XVII, (3.04 g, 83%) as a waxy solid.

60 MHz nmr ($CDCl_3$): δ 1.13 (double doublet, 2H, $J_{2_n,2_x}$ = 11-12 Hz, $J_{2_n,3_x}$ = 3-4 Hz, 2,3-endo protons), δ 2.04 (singlet, 3H, N-CH_3), δ 2.12 (multiplet, 2H, 2,3-exo protons), δ 4.02 (multiplet, 2H, 1,4-(bridgehead) protons), δ 7.12 (singlet, 4H, aromatic ring protons) see figure 20.

70 eV mass spectrum: m/e 159 (molecular ion), 132, 131 (base peak) 130 116, 90, 89, 63, 51 see figure 21.

IR (film), cm^{-1}: 3060 (m, =C-H), 2980 (m, C-H), 1260 (m, sh, C-N), 760 (s, 1,2-disubstituted aromatic ring).

N-Methyl-1,2,3,4-Tetrahydronaphthalen-1,4-imine-2,3-exo-d_2 (XVII-d_2)



The procedure for the synthesis of XVII was employed substituting LI-d_2 for II. Reduction of LI-d_2 (1.86 g, 8.5 mmoles), afforded XVII-d_2 XVII-d_2 (1.28 g, 93%).

60 MHz nmr ($CDCl_3$): δ 1.17 (singlet, 2H, 2,3-endo protons), δ 2.04 (singlet, 3H, N-CH_3), δ 4.05 (singlet, 2H, 1,4-(bridgehead) protons), δ 7.15 (singlet, 4H, aromatic ring protons) see figure 29a. To compare the nmr spectra of XVII and XVIIa-d_2, see figure 4, part II of this dissertation.

Benzenediazonium-2-Carboxylate

The procedure of Logullo et al.[159] was employed without change. The product was used in a subsequent reaction immediately upon isolation.

N-Methyl-2-Pyridone

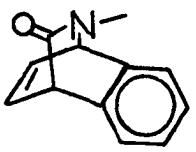
The procedure of Prill and McElvain[160] was employed without change.

N-Methyl-2-Pyridone-3,4,5,6-d_4

A procedure similar to the above was employed. Thus, dimethyl sulfate (37.8 g, 0.3 moles) was added to pyridine-d_5 (25 g, 0.3 moles) over a 15 minute period. The resulting mixture was heated on a steam bath for 2 hours, followed by addition of water (50 ml). $K_3Fe(CN)_6$ (196 g, 0.6 moles) in water (390 ml) and sodium hydroxide (49 g, 1.23 moles) in water (50 ml) were added to the pyridinium salt. Addition via separate dropping funnels was conducted so that the sodium hydroxide solution was completely added by the time 1/2 the $K_3Fe(CN)_6$ solution was added. During this addition the

reaction flask was maintained at less than 10° with a salt-ice bath. Two hours after complete addition the reaction mixture was saturated with sodium carbonate, then filtered and extracted with chloroform. After drying over sodium sulfate and removal of solvent, the crude product was vacuum distilled. The fraction boiling 116-118° at 9 torr (24.5 g, 73%) was > 98% N-methyl-2-pyridone-d_4 (gas chromatographic analysis). The 60 MHz nmr spectrum (neat solution) contained the N-methyl singlet as the only observable resonance.

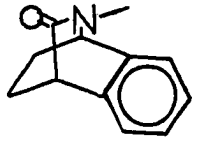
N-Methyl-1,4-Dihydro-1,4-Ethenoisoquinolin-3(2H)-one (LII)



N-Methyl-2-pyridone (5 g, 0.052 moles) and benzenediazonium-2-carboxylate [159] (from 0.05 moles anthranilic acid) were combined in dichloromethane (100 ml) and heated to reflux. Within one hour all of the benzenediazonium-2-carboxylate had dissolved, affording a dark but clear solution. After an additional 1-1/2 hours reflux the reaction was terminated. The black solution was washed with aqueous 5% potassium hydroxide (100 ml), then water (3 x 100 ml). Drying over sodium sulfate, then concentration on a rotary evaporator gave a heavy black oil which was chromatographed on neutral alumina. Elution with 3:1 hexane-ethyl acetate gave LII as an oil which was dissolved in ether and titurated with hexane to afford solid LII (1.1 g, 11%) After sublination at 100° and 0.1 torr, the colorless prouct melted 97-98° (lit[110] 98-100°).

LII-d_4 was produced in an analogous manner from 3,4,5,6-tetradeuterio-N-methyl-2-pyridone and benzenediazonium-2-carboxylate.

N-Methyl-1,4-Dihydro-1,4-Ethanoisoquinolin-3(2H)-one (LIII)

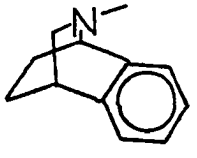


Compound LII (1 g, 5.4 mmoles) was dissolved in ethyl acetate (25 ml) and hydrogenated over 5% palladium on charcoal catalyst at 3 atmospheres H_2 pressure. After 1/2 hour the catalyst was filtered and the solution was concentrated to 5 ml. Tituration with hexane afforded LIII (0.93 g, 92%). Recrystallization from hexane gives colorless needles mp 130-131° (lit[109] 133-135 corrected).

Analysis for $C_{12}H_{13}NO$ (187.24): Calc. C 76.98, H 7.00 Found C 76.78, H 7.13.

LIII-d_6 was produced in an analogous manner from LII-d_4 via catalytic deuteration.

N-Methyl-1,2,3,4-Tetrahydro-1,4-Ethanoisoquinoline (XIX)



A solution of LIII (700 mg, 3.74 mmoles) in ether (10 ml) was added dropwise to lithium aluminum hydride (200 mg, excess) in ether (50 ml). The resultant mixture was refluxed for 8 hours, then quenched with water (5 drops), 15% aqueous sodium hydroxide (5 drops), and finally water (15 drops). After filtration of the aluminum salts, the ether solution was dried over sodium sulfate and concentrated in vacuo. Microdistillation at 55° and 0.1 torr afforded XIX as a colorless liquid (505 mg, 78%).

100 MHz nmr, $CDCl_3$: δ 1.37 (multiplet, 2H), δ 1.79 (multiplet, 1H) and δ 2.21 (multiplet, 1H)-ethano-bridge protons; δ 1.89 (doublet of triplets, 1H, J=13 Hz and ca 1-2 Hz, H_3syn), δ 1.98 (singlet, 3H, N-CH_3) δ 2.88 (multiplet, 1H, H_4) δ 3.28 (double doublet, J=13 Hz and J=1-2 Hz, 1H, H_3-anti), δ 3.49 (multiplet, 1H_9 H_1), δ 7.14 (multiplet, 4H, aromatic ring protons) see figure 26

70 eV mass spectrum: m/e 173 (molecular ion), 144 (base peak), 130, 115, 83, 77, 51 see figure 27.

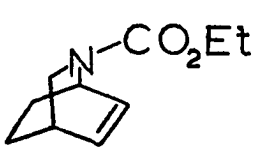
IR cm^{-1} (film): 2930 and 2850 (m, C-H) 1250 (br, w, C-N), 750 (sh, 1,2-disubtituted aromatic ring).

XIX-d_8 was prepared by the same method employing lithium aluminum deuteride reduction of LIII-d_6.

Methylenebisurethane

Urethane (178 g, 2.0 moles) and formaldehyde (81 g of 37% aqueous solution, 1 mole) were combine in cold water (1 liter) to which concentrated hydrochloric acid (2-3 ml) had been added. After 24 hours filtration afforded large colorless needles (110 g, 58%) and vacuum drying.

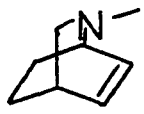
N-Carboethoxy-5-Azabicyclo(2.2.2)oct-2-ene



The procedure is similar to that of Cava et.al.[58] Methylenebisurethane (48 g, 0.25 moles) and boron-trifluoride etherate (10 g) were combined in benzene (500 ml) and set to reflux. Cyclohexadiene-1,3 (20 g, 0.25 moles) was added dropwise over a 45 minute period. After an additional 1.5 hours reflux, the reaction mixture was washed with saturated sodium bicarbonate (3 x 300 ml), followed by water (2 x 400 ml). The black oil obtained on concentration of the organic phase

was vacuum distilled. The product (11.3 g, 25%) was obtained from the fraction boiling at 83-85° (1.0 torr).

N-Methyl-5-Azabicyclo(2.2.2)oct-2-ene (XVIII)



N-carboethoxy-5-azabicyclo(2.2.2)oct-2-ene (17.6 g, 0.097 moles) was added dropwise to litium aluminum hydride (4.0 g, 0.1 moles) in ether (100 ml). After 8 hours reflux, the reaction was quenched with water (4 ml), 10% sodium hydroxide (12 ml) and again water (4 ml). After drying over sodium sulfate, the mixture was filtered and concentrated in vacuo. Distillation (58-60°, 10 torr) afforded N-methyl-5-azabicyclo(2.2.2)oct-2-ene (10.8 g, 91%).

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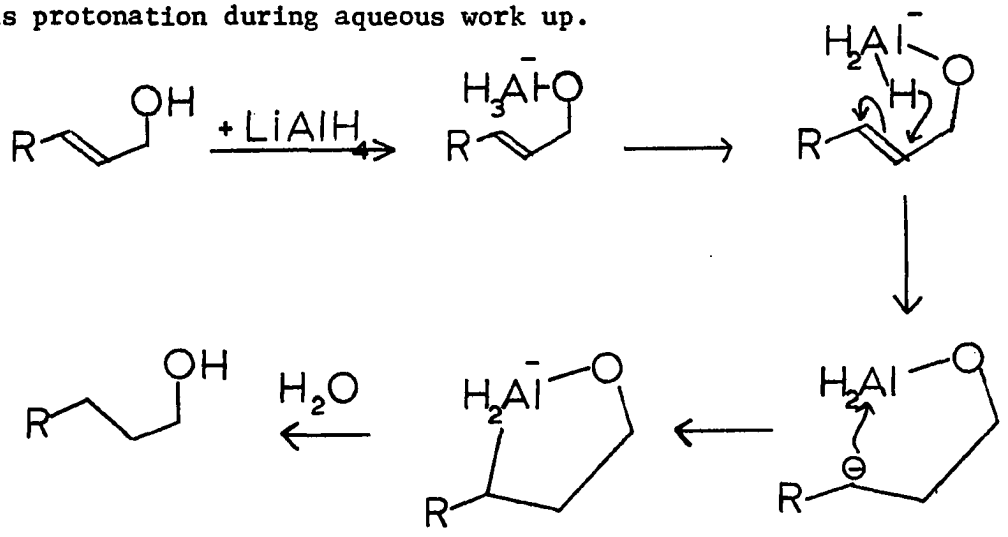
II. ANOMALOUS LITHIUM ALUMINUM HYDRIDE REDUCTION OF CARBON-CARBON DOUBLE BONDS IN 7-AZABICYCLO(2.2.1)HEPTENYL SYSTEMS

INTRODUCTION

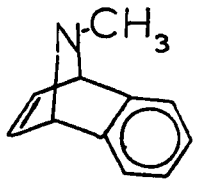
Recent interest in the mechanism of lithium aluminum hydride reductions of formally isolated carbon-carbon double bonds[1-5] prompted us to examine the mechanism of the corresponding reductions in azabicyclic systems.[6] Previous studies have shown that in certain allylic and propargylic alcohols, the double bond is reduced by LAH via an intramolecular hydride transfer. The initially formed organoaluminate transfers the hydride through a five membered transition state, with simultaneous/concomitant carbon-aluminum bond formation. The final step is protonation during aqueous work up.



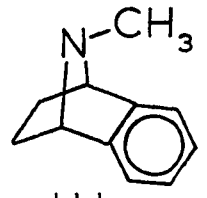
In this work we have examined the mechanism of LAH reduction of several bicyclic amine systems. Based on deuterium labeling studies we suggest mechanisms for the observed double bond reductions and differences in the reactivities of the bicyclic amine systems.

DISCUSSION AND RESULTS

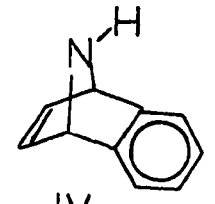
N-carboethoxy-7-aza-2,3-benzobicylo(2.2.1)heptadiene (1) was prepared via Diels Alder addition of benzyne to N-carboethoxypyrrole.[7] Reduction of I with LAH in refluxing ether for eight hours afforded the desired N-methyl-7-aza-2,3-benzobicyclo(2.2.1)heptadiene[8] (II) in poor yield, along with two other components. This product mixture was separated by gas chromatography on a 3 m by 0.635 cm 20% FFAP column (temperature $\leq$ 150°, Helium flow rate = 120 ml/min).[9] By a combination of nmr and mass spectrometry the two remaining products were identified as N-methyl-7-aza-2,3-benzobicyclo(2.2.1)heptene,[7] III and 7-aza-2,3-benzobicyclo(2.2.1)heptadiene,[11] IV.



II



III



IV

The nmr and mass spectra of II-IV are shown in Figures 1-3 respectively.

Once these compounds were identified the product distribution could be obtained from integration of the gc trace or directly from the nmr of the crude mixture of products. (The chemical shifts of the bridgehead protons of II-IV are sufficiently unique to allow product ratio determination).

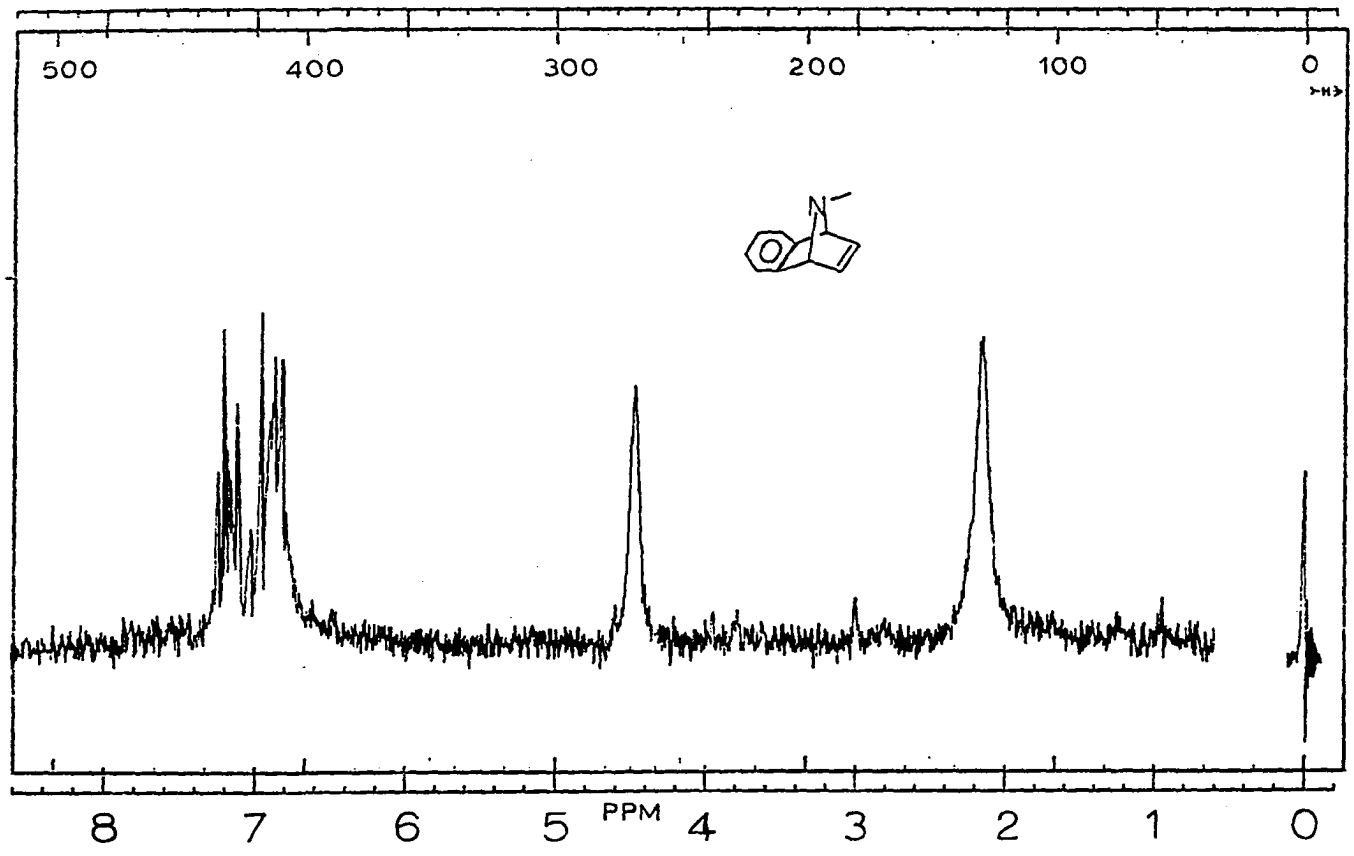


Figure 1a. 60 MHz nmr spectrum of II, $CDCl_3$

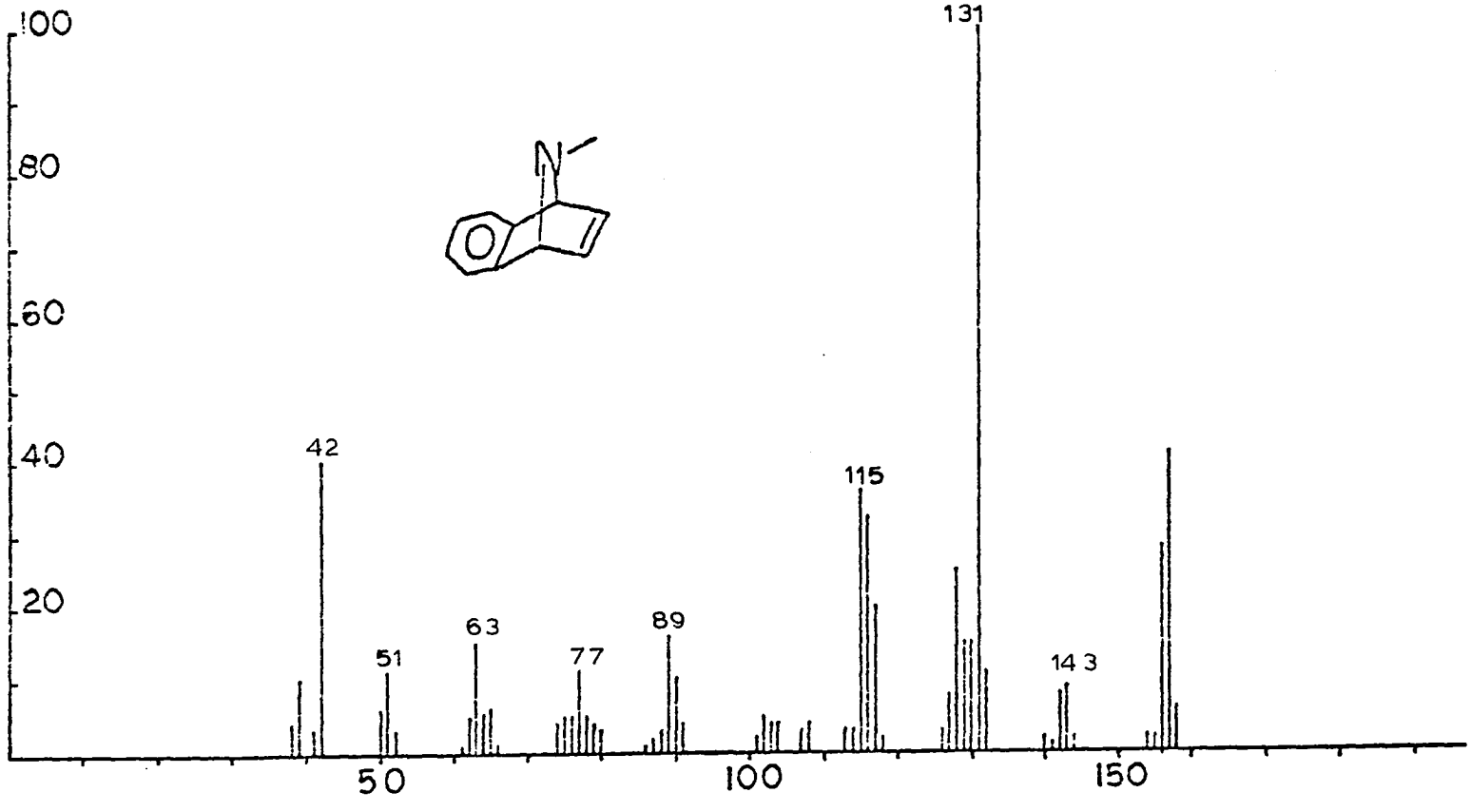


Figure 1b. 70 eV mass spectrum of II

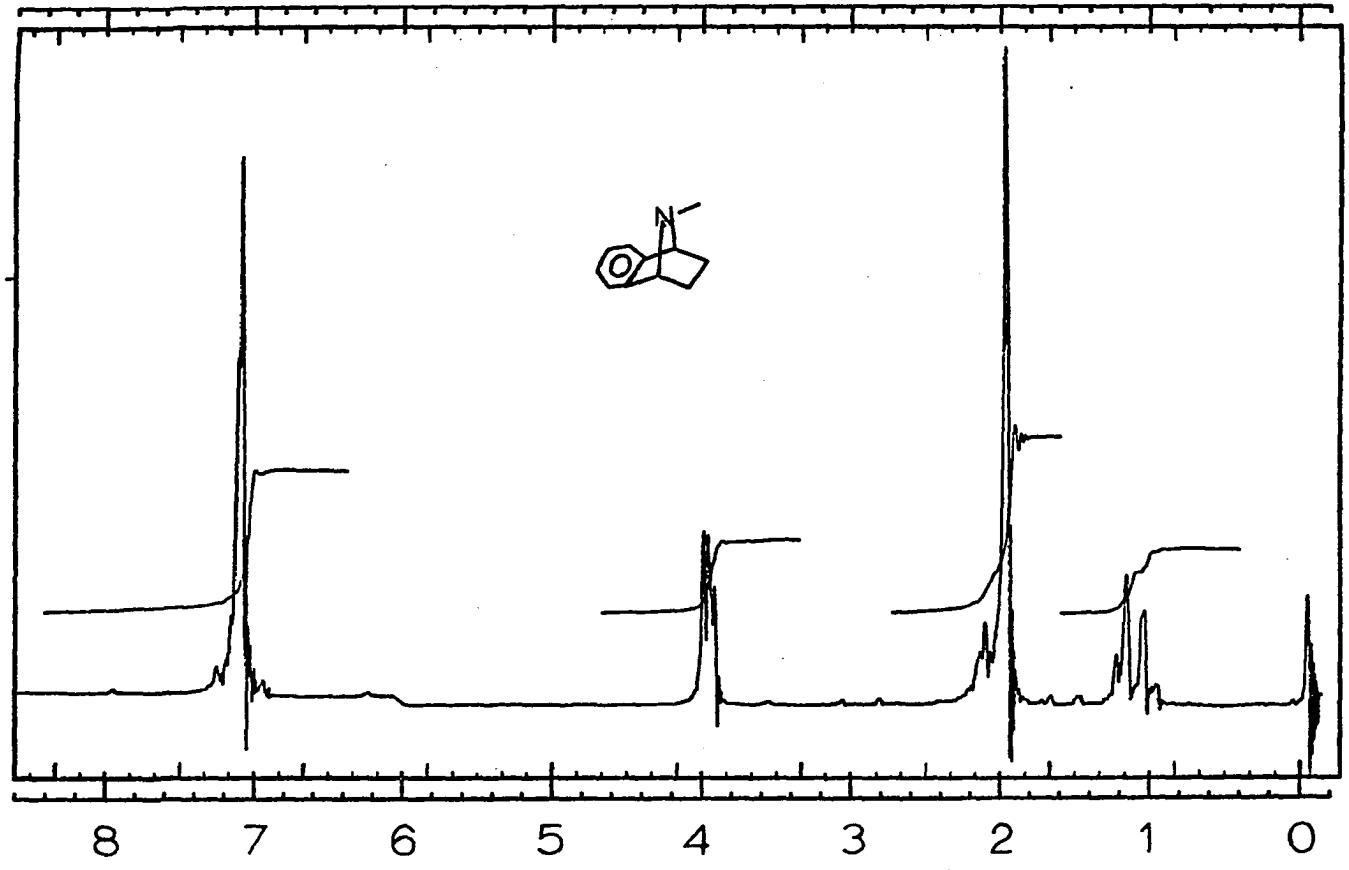


Figure 2a. 60 MHz nmr spectrum of III, $CDCl_3$

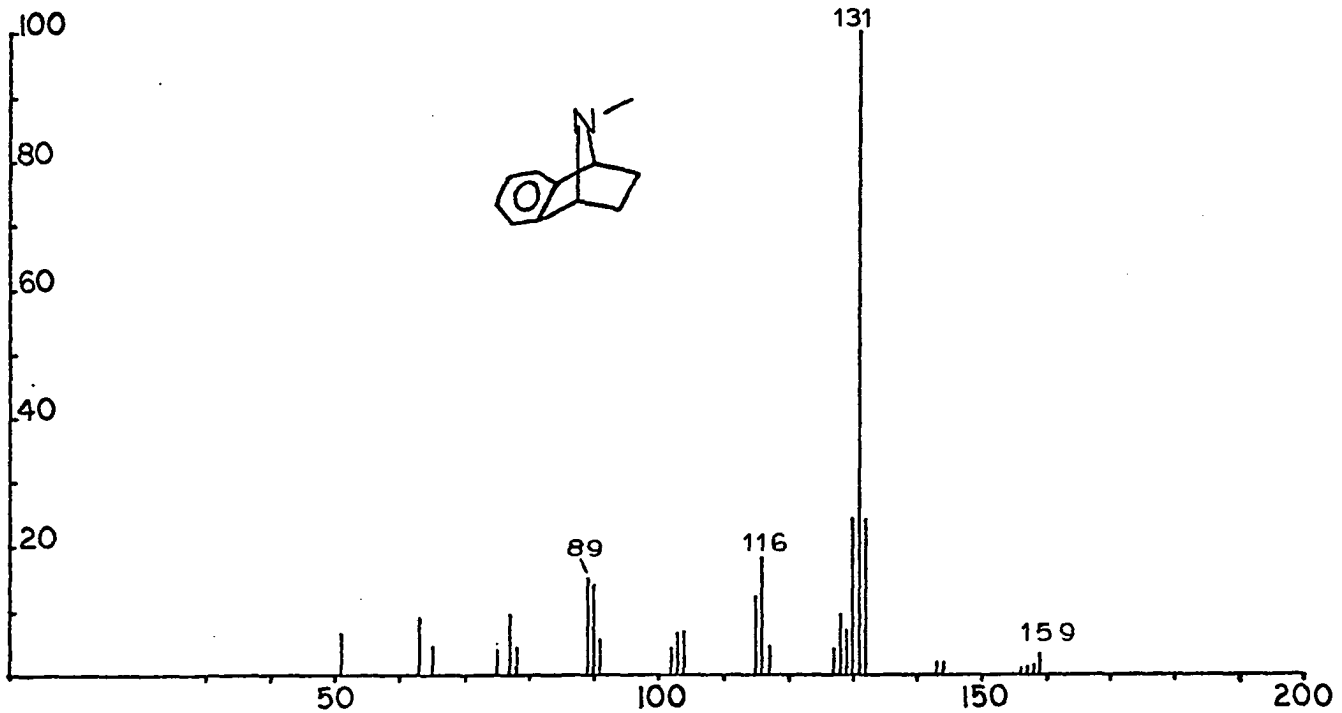


Figure 2b. 70 eV mass spectrum of III

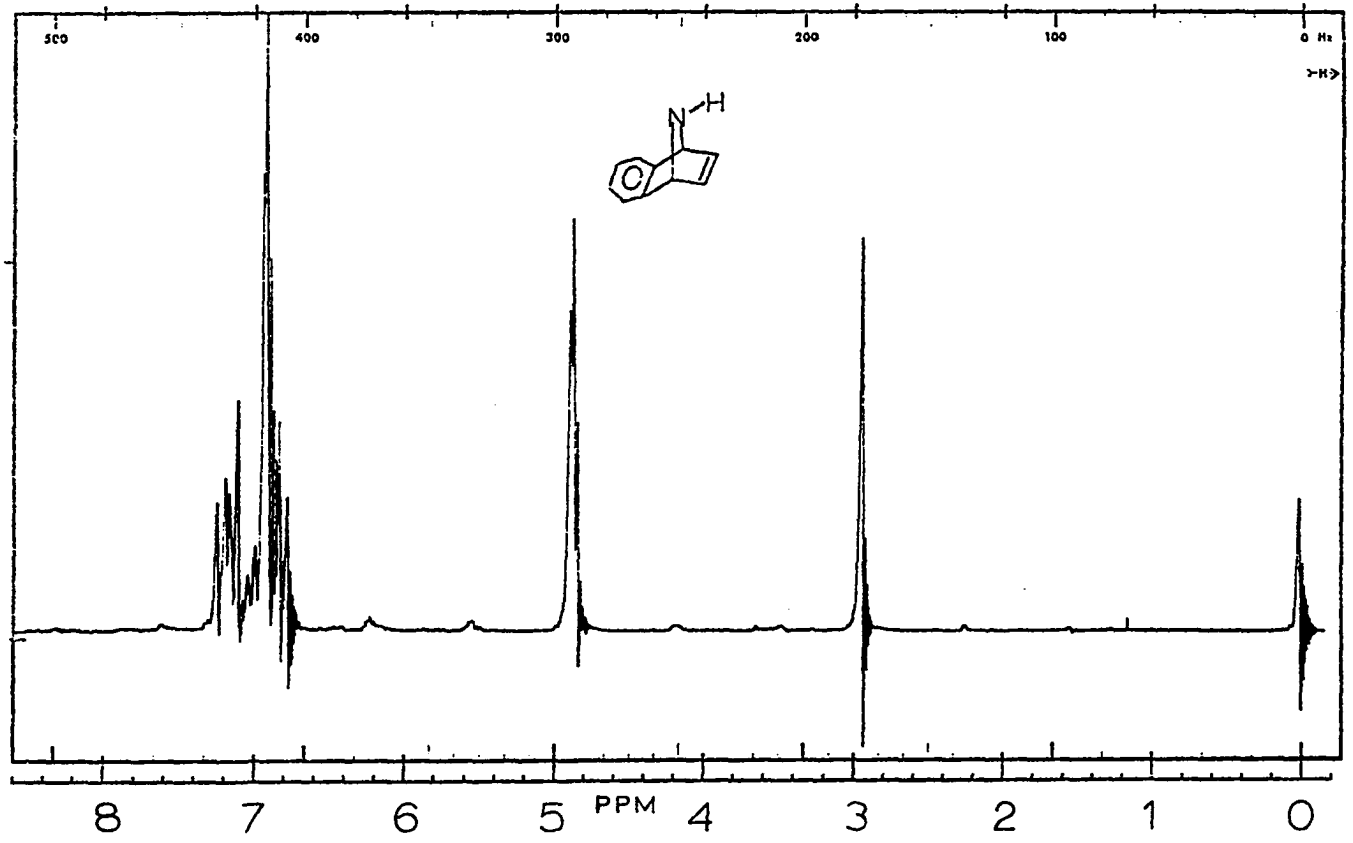


Figure 3a. 60 MHz nmr spectrum of IV, $CDCl_3$

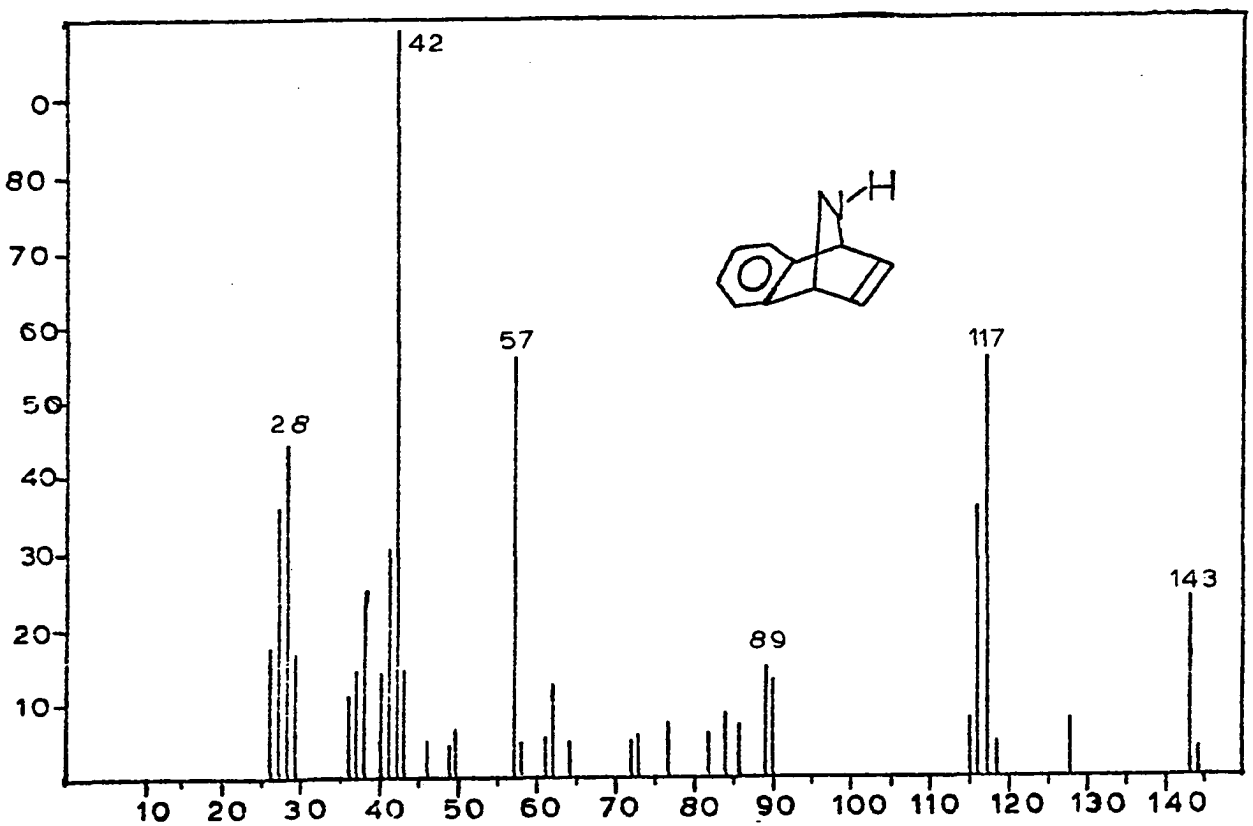
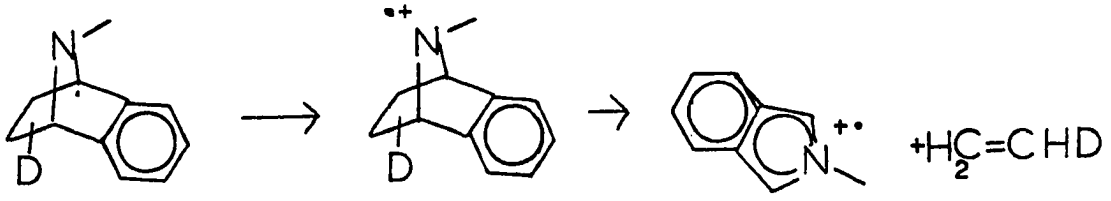


Figure 3b. 70 eV mass spectrum of IV

We employed deuterium labeling to delineate the mechanism of double bond reduction. LAH reduction of I followed by workup with $NaOD/D_2O$ afforded III-d_1 along with II and IV. Mass spectral analysis of III-d_1 indicated greater than 91% d_1. Furthermore, the deuterium atom must be on the 5 (or 6) carbon, based on the fact that deuterium is absent from the base peak, (for several of the bicyclic amines studied, the base peak corresponds to loss of ethylene, a retro-Diels-Alder reaction).



m/e 160 me/ 131 m/e 29

Integration of the nmr of III-d_1 indicated a two to one ratio of <u>endo</u> to <u>exo</u> protons, indicating <u>exo</u> deuterium substitution. This was further substantiated by the coupling patterns of both the <u>endo</u> and bridgehead protons. The bridgehead ($H_{1,4}$) and <u>endo</u>-5,6 protons are not spin coupled (dihedral angle = 90°); therefore, <u>endo</u> deuterium substitution would have little effect on the coupling pattern of the bridgehead protons. Inspection of Figure 4a and 4b clearly indicates that the bridgehead and <u>endo</u> proton coupling patterns are perturbed; therefore deuterium substitution must be <u>exo</u>. (compare with 4c[7])

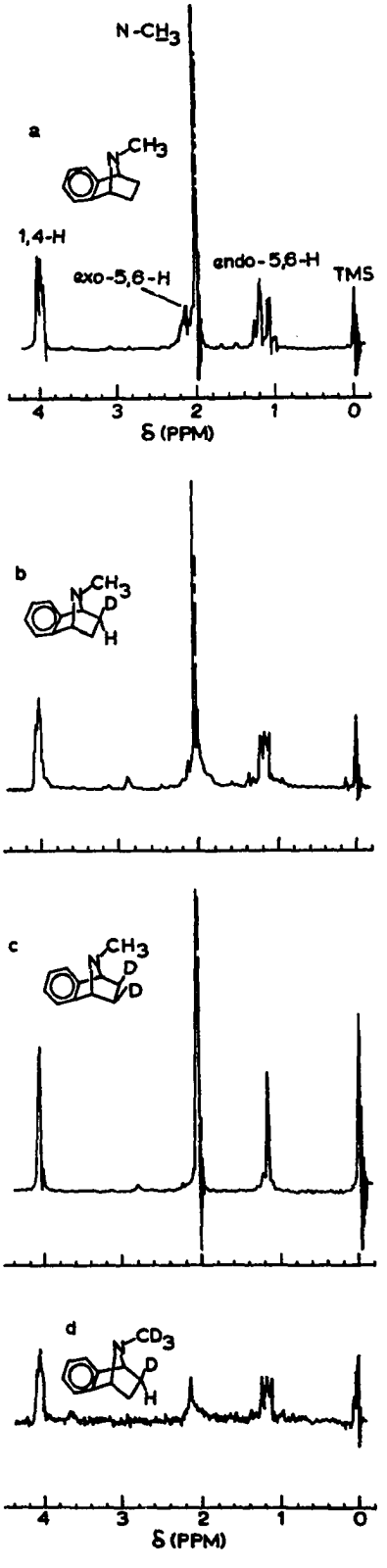
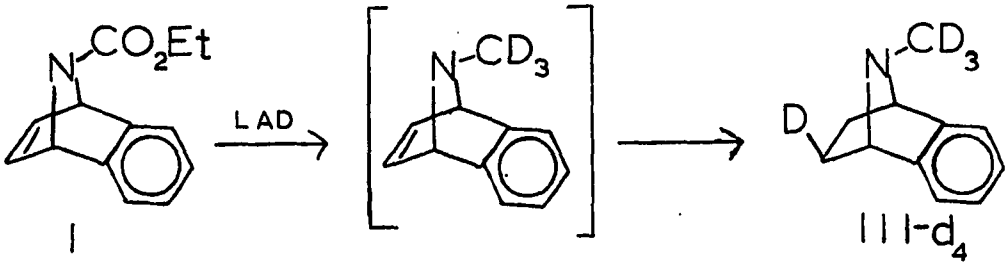


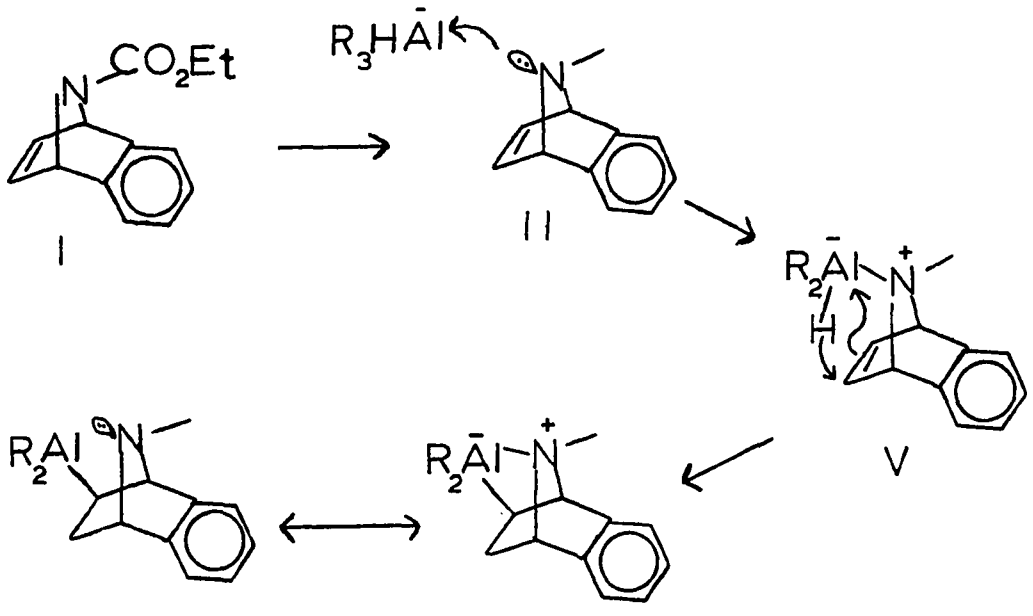
Figure 4. Partial 60 MHz nmr spectrum of III, III-d_1, III-d_2, and III-d_4.

As a complement to the above experiment another reduction was performed employing LAD and $NaOH/H_2O$ workup. Mass spectral and nmr analysis showed the product to be III-d_4. Three deuterium atoms were contained in a CD_3 group, while the remaining deuterium was incorporated into the exo-5(or6) position. (see Fig 4d) In a separate experiment, II was treated under conditions whereby I is reduced to II-IV. By monitoring the reaction by gas chromatography, we determined that II was completely reduced to III.



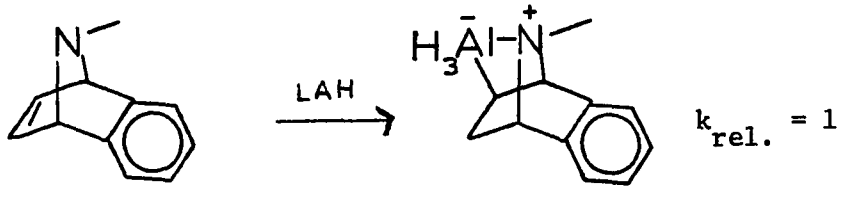
I III-d_4

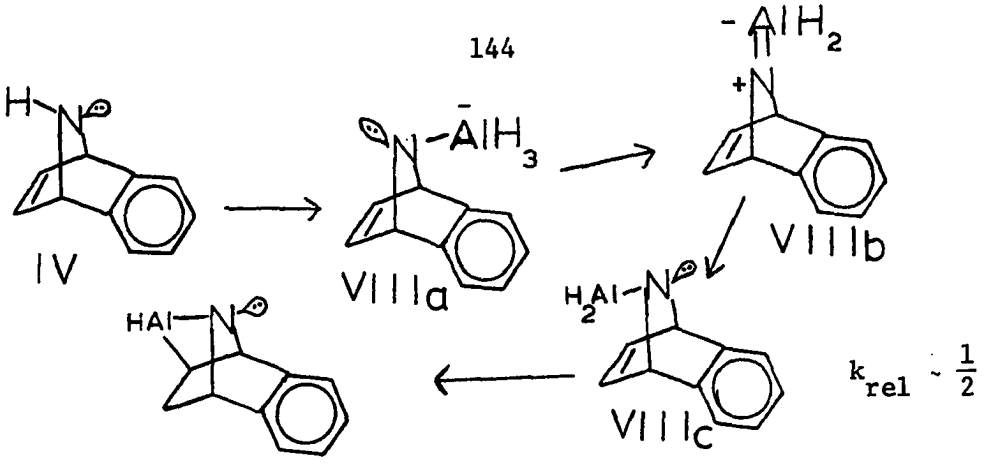
This result suggests that II may be an intermediate in the overall reduction of I to III. A mechanism which is consistent with the aforementioned results is outlined below. Initial reduction of I to II results in complex formation between the nitrogen and aluminum atoms (V). Intramolecular hydride transfer occurs via a four member transistion state (or intermediate), VIa. Finally, protonolysis of the carbon-aluminum bond (which occurs stereospecifically with retention of configuration)[10] during aqueous workup afforded III.



Intermediate

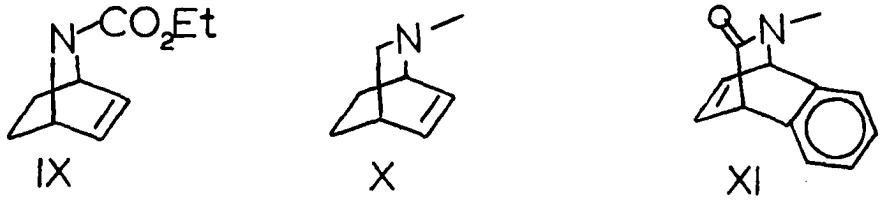
Interestingly, we observed no 7-aza-2,3-benzobicyclo(2.2.1) heptene[11] (VII) among the products of reduction of I. In a separate experiment, reduction of IV to VII occured under conditions whereby II is reduced to III. However, the reduction of IV to VII was somewhat more sluggish than the corresponding reduction of II to III. For comparable conditions (stoichiometric ratio of amine to LAH, concentration, and temperature) the reduction of IV to VII required about twice the time as the corresponding reduction of II to III. This retarded reaction rate may be due to stabilization of the sp^2 hybridized nitrogen-aluminum intermediate VIIIb, relative to VIIIa or VIIIc.

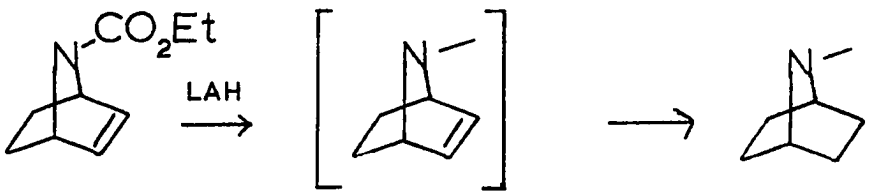


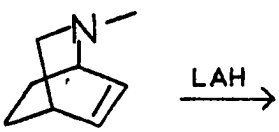


In conformation VIIIb (or a) intramolecular hydride donation to the double bond is not possible. The rate of double bond reduction is dependent on the concentration of VIIIc; therefore stabilization of VIIIb will decrease the concentration and hence rate of reduction of IV.

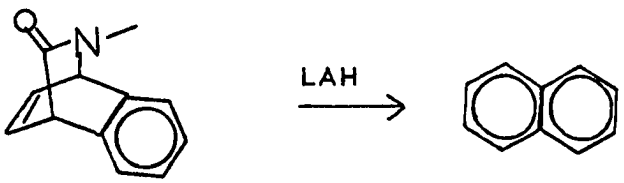
We have extended our studies to include three related systems: N-carboethoxy-7-azabicyclo(2.2.1)hept-2-ene (IX),[7] N-methyl-5-azabicyclo (2.2.2)oct-2-ene (X)[12] and N-methyl-6-oxo-5-aza-2,3-benzobicyclo(2.2.2)-octadiene (XI)[13]. As previously noted in part I of this dissertation, complete reduction of the double bond in IX occurs under conditions which yield only partial reduction of the double bond in I. However, similar treatment of X with LAH-Et_2O resulted in no double bond reduction whatsoever! To further complicate matters, similar treatment of XI with LAD-Et_2O resulted in the formation of naphthalene as the sole product! (vide infra)







no reaction



Double bond reduction in the (2.2.1) but not the (2.2.2) amines appears to indicate that the necessary conditions for double bond reduction are twofold: An electronegative substitutent must be in a position such that coordination with aluminum allows close physical proximity to the double bond and this double bond must be activated due to strain. The fact that the (2.2.2) amine suffered no double bond reduction can be explained by considering the difference in the strain between double bonds in the (2.2.2) amine vis-a-vis the (2.2.1) amine. A comparison with carbocyclic analogues is illuminative.

Turner and coworkers[14] determined the heats of hydrogenation for bicyclo(2.2.1)heptene, bicyclo(2.2.1)heptadiene, bicyclo(2.2.2) octene, and bicyclo(2.2.2)octadiene, which are listed in Table I. The difference in the heats of hydrogenation between the (2.2.1) and

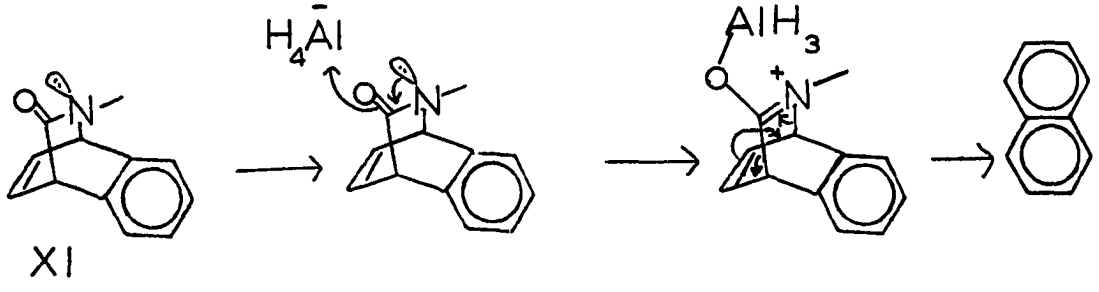
TABLE I

Compound	ΔH_H heat of hydrogenation, kcal/mole
bicyclo(2.2.1)heptene	
	-33.1
bicyclo(2.2.1)heptadiene	
	-68.1 (-35.0)[a]
bicyclo(2.2.2)octene	
	-28.3
bicyclo(2.2.2)octadiene	
	-56.2 (-27.9)[a]

a. Values in paraenthesis are the calculated ΔH_H of the first double bond. ΔH_H(diene)-ΔH_H(ene)

(2.2.2) series can be considered to be a measure of strain in the double bonds. For reduction of the first double bond of the dienes, norbornadiene liberates 7.1 kcal/mole more energy than bicyclo(2.2.2)octadiene. Similarly, reduction of the second double bond indicates that norbornene is 4.8 kcal/mole more strained than bicyclo(2.2.2)octene. The relief of strain which occurs upon saturation of the double bond in the (2.2.1) alkene is considerably greater than is the corresponding strain relief in the (2.2.2) systems. The 5 to 7 kcal/mole energy difference suggests a reasonable explanation for the different reactivities which our bicyclic amine systems reveal toward LAH-Et_2O.

The mechanism of the aberrant reduction of XI was not pursued. However, one control experiment was run. Refluxing XI in ether for 24 hours without LAH left it unchanged. This confirmed that the reaction in the presence of LAH is not just a thermal retro-Diels-Alder reaction. One possible explanation for the production of naphthalene from XI is shown below.



Complexation of the carbonyl oxygen to aluminum with concomitant lone pair donation by nitrogen leads to a more strained system. This excess strain thereby provides the driving force for a retro-Diels-Alder reaction (which affords N-methyl ketenimine and naphthalene).

SUMMARY

In this work we have examined the mechanism of reduction of several azabicyclic compounds by means of deuterium labeling. Our results suggest that the requirements for reduction of a formally isolated double bond are twofold: The geometry of the nitrogen-aluminum complex must place an aluminum hydride bond in close physical proximity to the double bond, and this bond must be activated somewhat by strain.

EXPERIMENTAL

Reduction of N-carboethoxy 7-azabenzobicyclo(2.2.1)heptadiene I.[7]

An ether solution of 4.65 mmoles I was added dropwise to 4 mmoles LAH (or LAD) in gently refluxing ether. After 8 hours, tlc (20% EtOAc/Hexane eluent) indicated complete reaction of I. The reaction was quenched by successive addition of 4 drops $H_2O(D_2O)$, 4 drops 10% NaOH(NaOD), and 10 drops $H_2O(D_2O)$. After filtration of the solid aluminum salts and drying over Na_2SO_4, the product mixture was separated by gas chromatography on a 3 m by 0.635 cm 20% FFAP column (temp = 150° flow rate 120 ml/min). The relative yields and retention times of II through IV were: II, 33% (4.6 min) III 61% (8.6 min) and IV, 6% (14.8 min).

Reduction of III to II or IV to VII.

Approximately 50 mg of the amine was treated with two equivalents LAH in refluxing Et_2O. The reactions were monitored by gas chromatography (vide supra). Whereas the reduction of III to II was complete in 4-5 hours, the corresponding reduction of IV to VII was not complete after 10 hours.

Attempted reduction of X.

Treatment of X in the manner described above for II and IV showed no reaction after 24 hours. The reaction was monitored by removing a one ml aliquot, quenching with one drop 10% NaOH, and drying over Na_2SO_4. This solution was then subjected to gas chromatography. The retention time of the reaction product was compared to that of N-methyl-2-azabicyclo(2.2.2)octane[12] prepared by catalytic hydrogenation of X.

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7. For preparation, see experimental section, Part I.

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9. Due to a facile retro 4+2 reaction on hot metallic surfaces, it is necessary to also cool the injector and detector blocks to ~150°.

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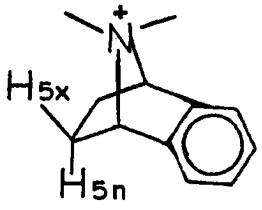
III. ANGULAR DEPENDENCE OF VICINAL ^{14}N-H COUPLING CONSTANTS IN BICYCLIC AMMONIUM SALTS

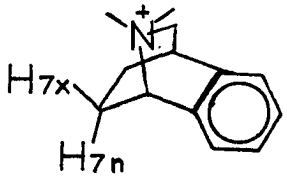
INTRODUCTION

Due to rapid relaxation of the ^{14}N nucleus, most ^{14}N-H spin coupling is unobserved. This is a result of the inverse relationship of the relaxation time, T_1, and the nmr line width. Spin coupling between protons and ^{14}N is observed in certain quaternary ammonium salts where T_1 is much longer. Vicinal spin coupling, $^3J_{^{14}N-H}$, has been observed in both cyclic[1] and acyclic[2-4] alkyl ammonium salts and enammonium salts.[5-10] In acyclic quaternary ammonium salts, the vicinal coupling constants vary from ca. 1.62 to 2.10 Hz and are independent of the counter ion.[11] In quaternary alkyl ammonium salts where the stereochemistry of vicinal ^{14}N and ^{1}H atoms is accurately known, the magnitude of $^3J_{N-H}$ was shown to be dependent upon the dihedral angle, ϕ.[1] The exact relationship between the dihedral angle and the absolute value of $^3J_{N-H}$ was not obtained by Tori and co-workers because they were unable to account for the effect of adjacent electronegative substituents.[12,13] In this work we have examined several vicinal spin

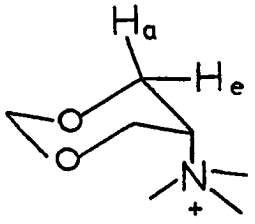
couplings, $^{3}J_{N-H}$, in systems I-V. From a plot of J vs angle Ø we show that a Karplus type relationship is followed, as has been suggested for other vicinal proton-heteroatom spin couplings.[15] (such as $J_{13_{C-H}}$, $J_{29_{Si-H}}$ and $J_{31_{P-H}}$)



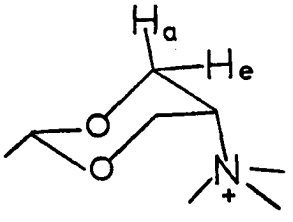
I



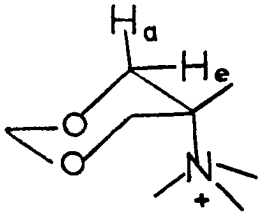
II



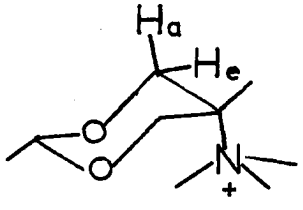
IIIa



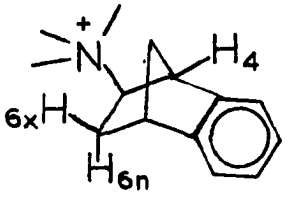
IIIb



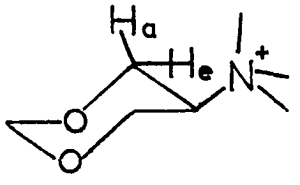
IIIc



IIId



IV



V

DISCUSSION

Both direct and indirect (via coupling with other nuclei) observation of nitrogren spin coupling has been hindered for several reasons. Both ^{14}N and ^{15}N are intrinsically less sensitive to the nmr experiment than are protons; hence, direct observation is difficult, (the ^{14}N nucleus is only 10^{-3} as sensitive as is the ^{1}H nucleus). For ^{14}N (which possesses an integral spin quantum number), rapid quadrupolar relaxation washes out spin coupling and obfuscates indirect observation in all but a few limited situations (vide infra). On the other hand, ^{15}N has no quadrupolar relaxation to broaden the nmr signal (^{15}N nuclear spin quantum number = 1/2). However, its low natural abundance (0.37%) prevents its being observed except in isotopically enriched samples.[16,17] With present technology and price limitations, the most practical method of observing spin coupling to nitrogen is an indirect method involving ^{14}N and a more sensitive nucleus. If a coupling constant for either ^{14}N or ^{15}N can be determined empirically, the corresponding coupling constant for the remaining N-nucleus can be calculated from the relationship

$$\frac{\gamma_{^{14}N}}{\gamma_{^{15}N}} = \frac{J_{^{14}N-X}}{J_{^{15}N-X}} = -0.713$$

where γ_{a_N} is the gyromagnetic ratio of the a^{th} isotope.

The overriding problem associated with observation of proton coupling to the ^{14}N nucleus results from the quadrupolar relaxation.[18] For nuclei with spin quantum numbers greater than 1/2, a nonsysmmetric electric field gradient is possible. For those nuclei the quadrapole moment may align with the applied magnetic field and thereby provide a mechanism for rapid relaxation in the cases of the quadrupolar nuclei and any other nuclei coupled to it. The relaxation time, T_1, is inversely proportional to the observed linewidths; therefore, short relaxation times lead to broad nmr signals. Spin coupling of protons to nitrogen is generally not observed because the magnitude of line broadening due to quadrupolar relaxation is greater than the magnitude of spin coupling.[19] Quadrupolar line broadening become much less favorable in the presence of a symmetrical electric field gradient at the ^{14}N nucleus. This is of course due to the absence of a quadrupole moment, which, increases the spin lattice relaxation time, thereby affording sharper lines in both the proton and ^{14}N nmr spectrum.[20] The effect of asymmetry in the electric field gradient at nitrogen is apparent in the normal and nitrogen decoupled proton nmr of N-methyl 7-aza-2,3-benzonorbornene. No difference in the two spectra (and hence no ^{14}N-^{1}H coupling) was observed. Examination of the normal and nitrogen decoupled proton nmr of the corresponding methiodide (I) however, clearly shows the presence of spin coupling between nitrogen and the 5,6-endo protons. (see Figure 1)

Even for the fairly symmetric methiodide I, some quadrupolar line broadening occurs, at the ambient probe temperature (30°). The nmr spectrum can be measurably improved by simply increasing the temperature,

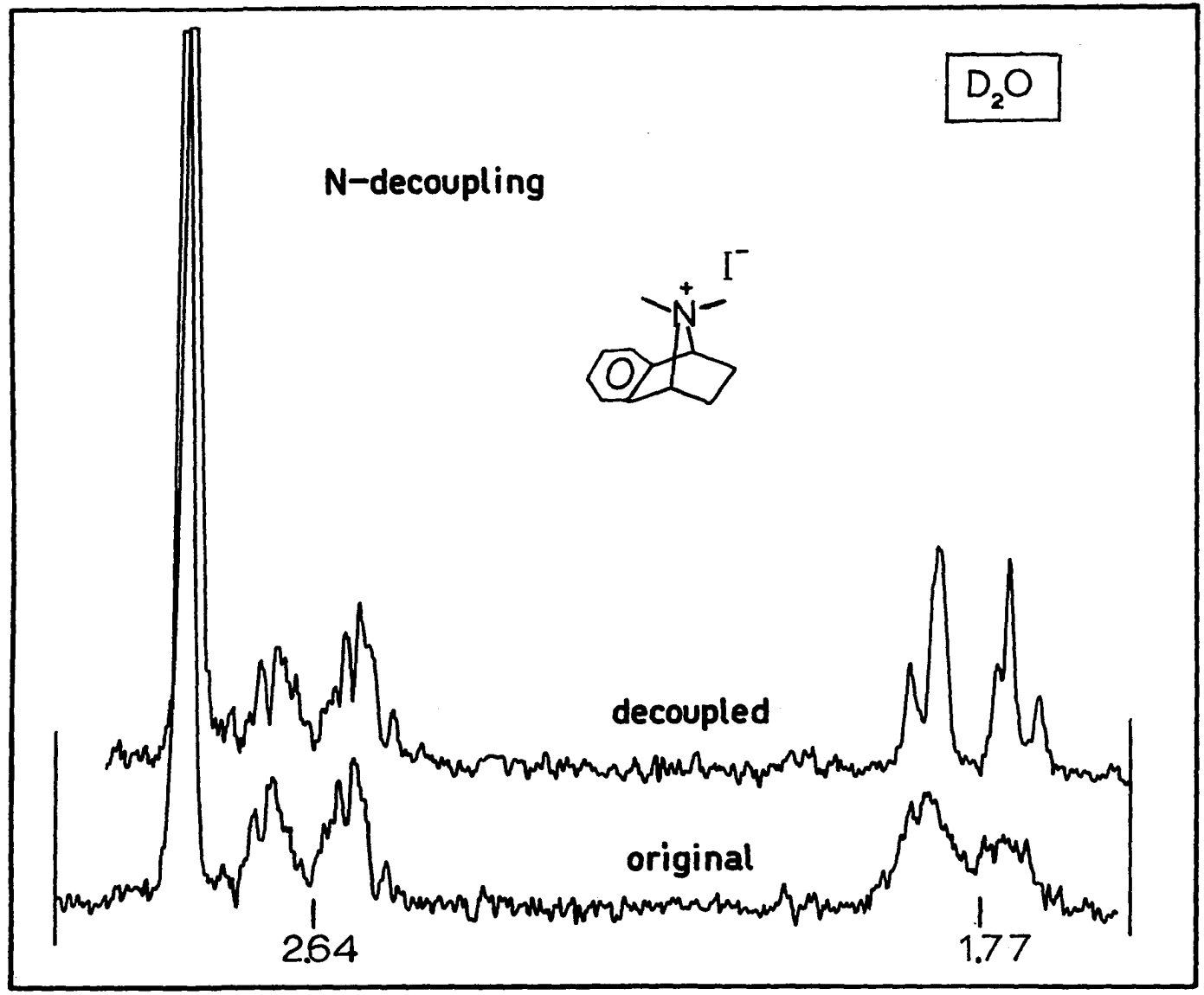
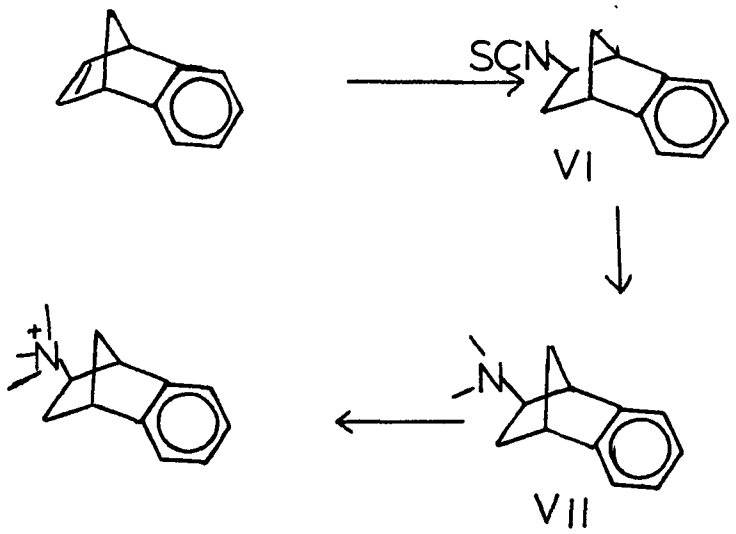


Figure 1. Normal and ^{14}N-decoupled partial 100 MHz nmr spectrum of I, D_2O.

due to the inverse temperature dependence of quadrupolar relaxation.[21,22] Figure 2 shows the proton nmr of the 5,6 exo and endo proton region of I at 30 and 85°.

Before considering the results of the $^{3}J_{N-H}$ coupling constant measurements, a brief digression will be made to discuss the preparation of compounds I, II, and IV. Preparation of the immediate precursors of I and II, N-methyl-7-aza-2,3-benzonorbornene and N-methyl-5-aza-2,3-benzobicyclo(2.2.2)octene respectively, have been discussed in part I. The methiodides I and II, were obtained by addition of the free base to excess methyl iodide in chloroform solution. The solid quaternary salt, which formed immediately was filtered from solution, dried, and then used without further purification. The 300 MHz proton nmr of I and II are shown in figures 3 and 4, respectively. Compound IV, 5-exo trimethylammonium-2,3-benzonorborneneiodide was prepared by the method outlined in scheme I.

Scheme I



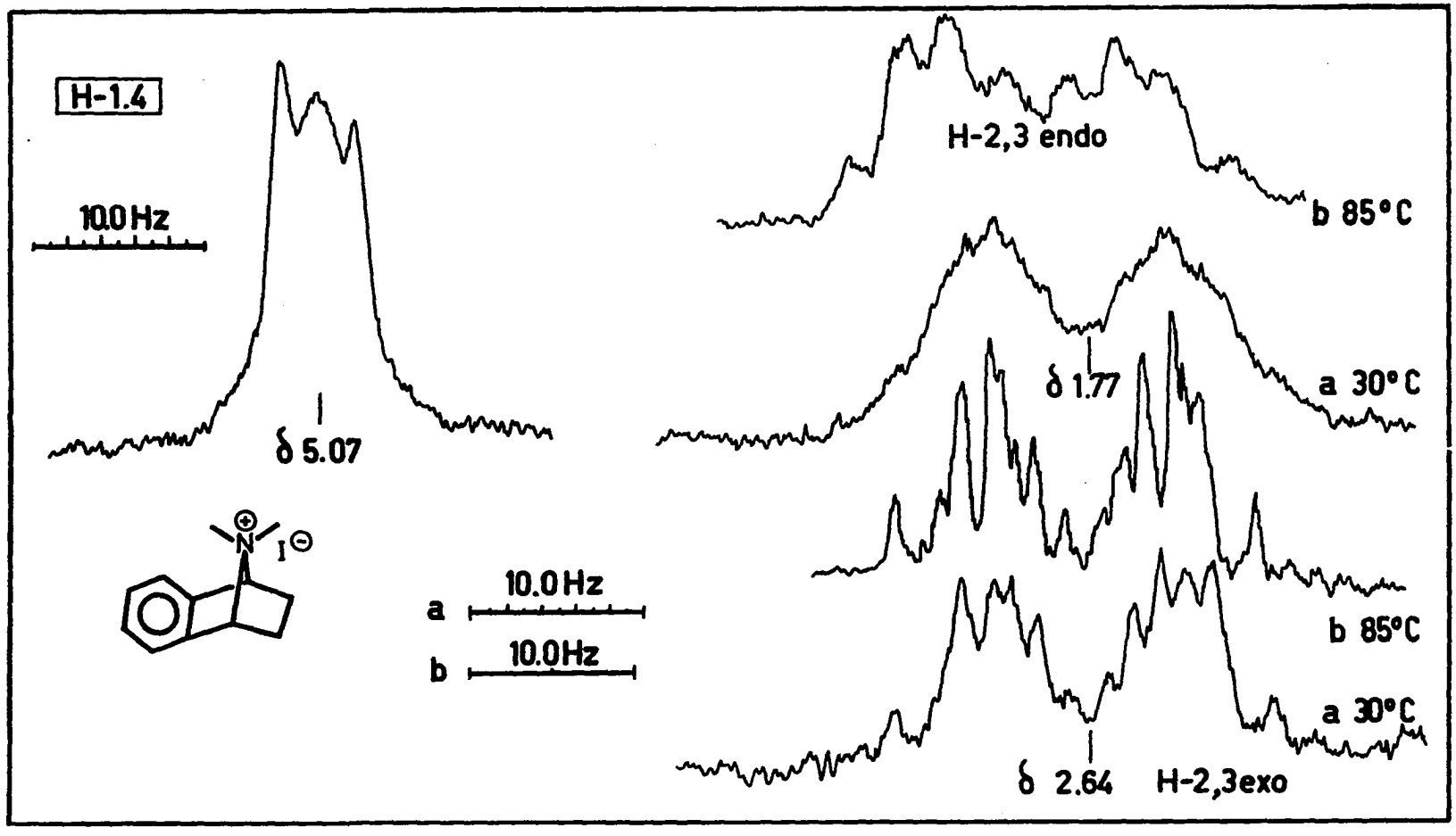


Figure 2. Temperature dependence-partial 100 MHz nmr spectrum of I, D_2O.

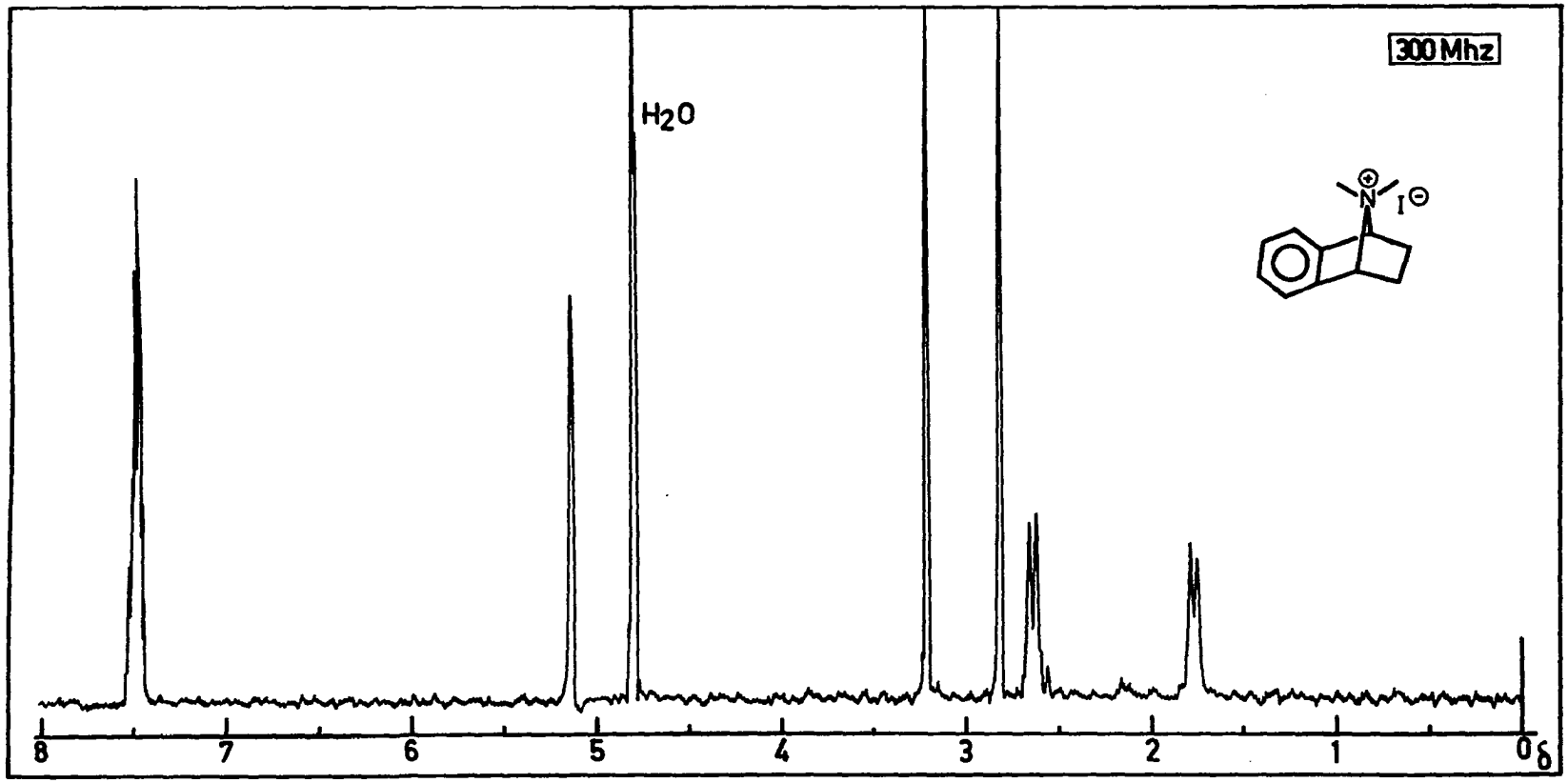


Figure 3. 300 MHz nmr spectrum of I, D_2O.

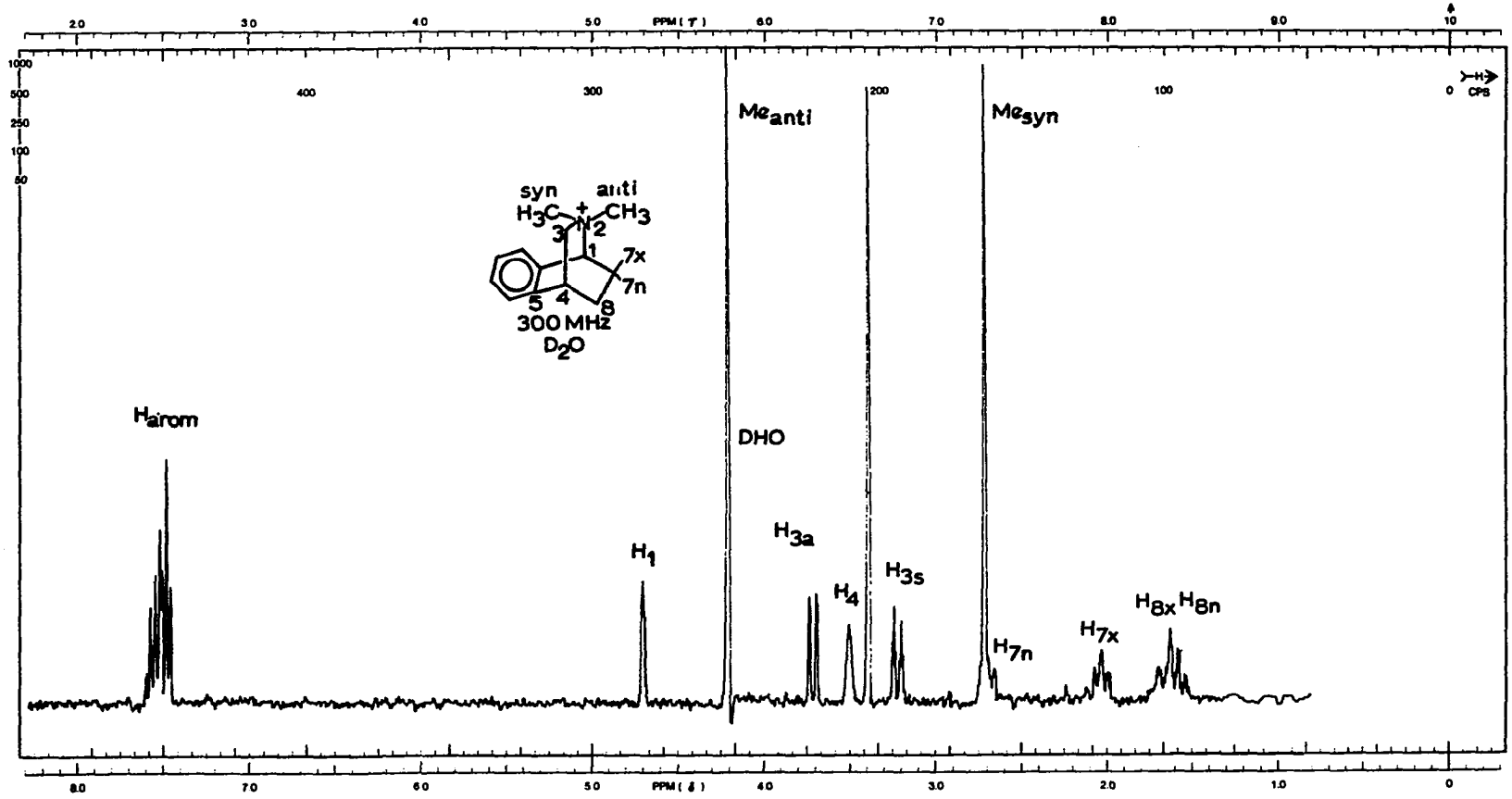
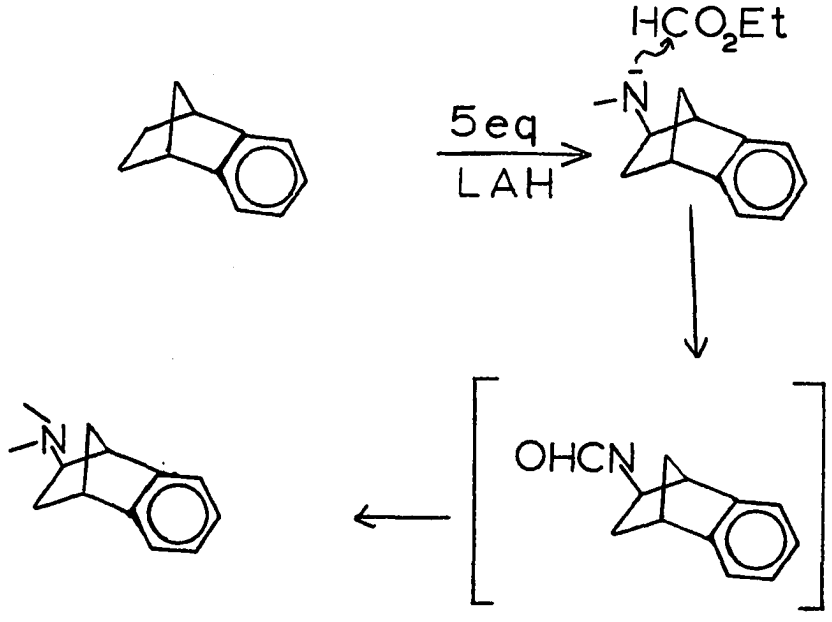


Figure 4. 300 MHz nmr spectrum of II, D_2O.

Acid catalyzed addition of isothiocyanic acid to benzonorbornadiene[23] gave the desired exo-5-isothiocyanate VI as the only product in 83% yield. The configuration of the isothiocyanate moiety was assumed to be exo, based on the known stereospecificity of addition to the norbornyl cation.[24,25] The conformational assignment was confirmed on observation of the nmr of IV (vide infra).

The proton nmr and mass spectra of VI are presented in Figures 5 and 6 respectively. Production of VII, exo-5-dimethylamino-2,3-benzonorbornene, from VI in a "one pot" reaction represents a rather novel reductive alkylation. In 1962, Wright[26] presented evidence that lithium (or aluminum) salts of dialkyl amines in the presence of excess LAH, react with methyl formate to yield dialkylformamides. These are subsequently reduced to the methyl dialkyl amines in good yield. Following Wright's suggestion, Scheme 2 outlines our synthesis of VII.

Scheme 2



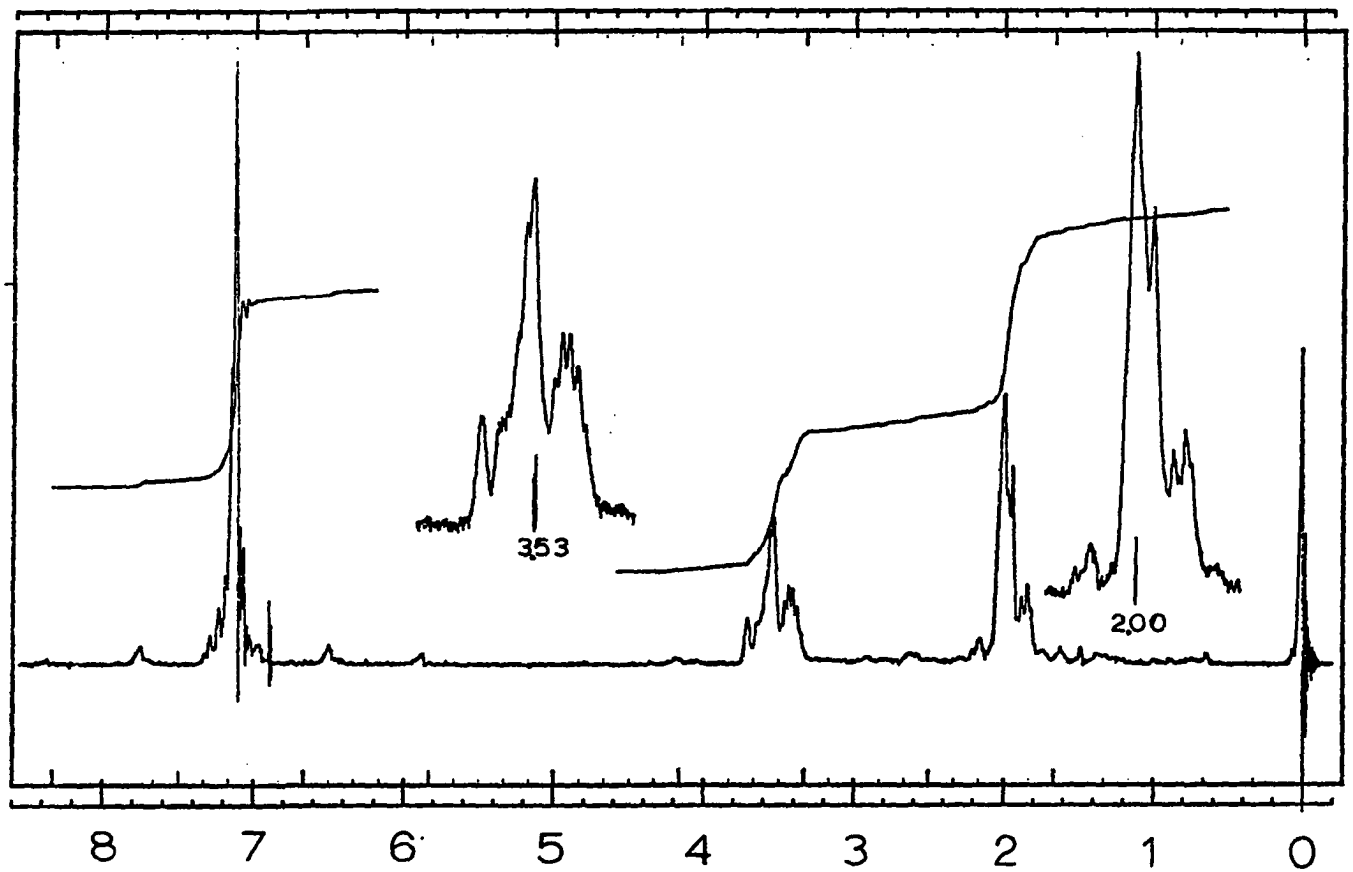


Figure 5. 60 MHz proton nmr spectrum of VI, $CDCl_3$

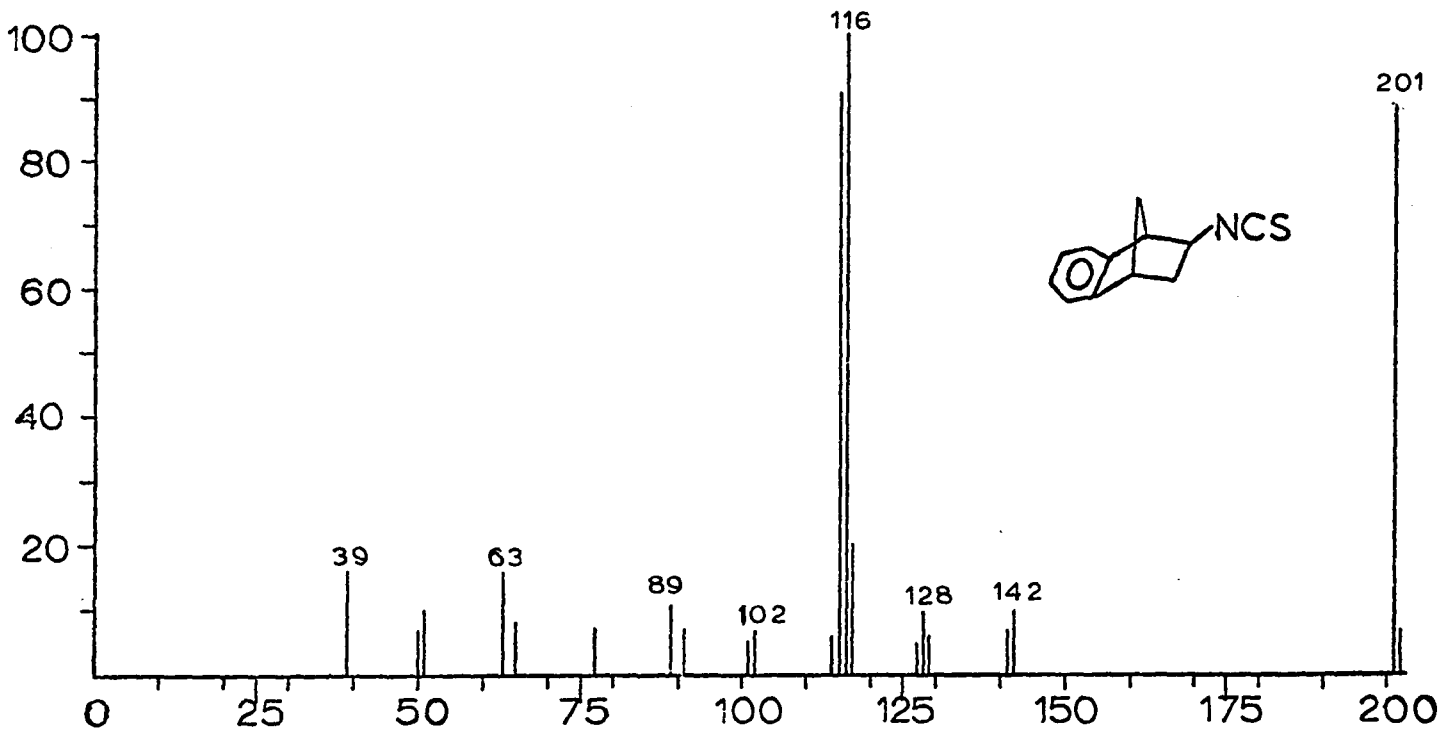
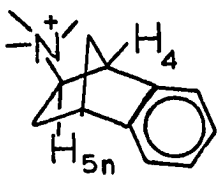


Figure 6. 70 eV mass spectrum of VI

Addition of VI to 5 equivalents LAH reduced the isothiocyanate to the lithium (or aluminum) alkyl methyl amide, leaving two equivalents of unreacted LAH. Addition of one equivalent of ethyl formate produced the formamide *in situ*, which was subsequently reduced by the two remaining equivalents of LAH to give a 47% yield of VII. Figures 7 and 8 are the proton nmr and mass spectra respectively of VII.

Treatment of VII with MeI as noted for compounds I and II yielded IV quantitatively. Assignment of the *exo* configuration at C5 to structures VI, VII, and IV is confirmed by examining the 300 MHz proton nmr of IV in D_2O. (Figure 9) The "singlet" at *ca*. 3.9 ppm (H_4) and "triplet" at *ca*. 3.4 ppm (H_5 endo) are only consistent with an *exo* substitutent at C_5.



$J_{H_{5_n}-H_4} \simeq 0$

H_{5_n} coupled only to H_{6_x} and H_{6_n}

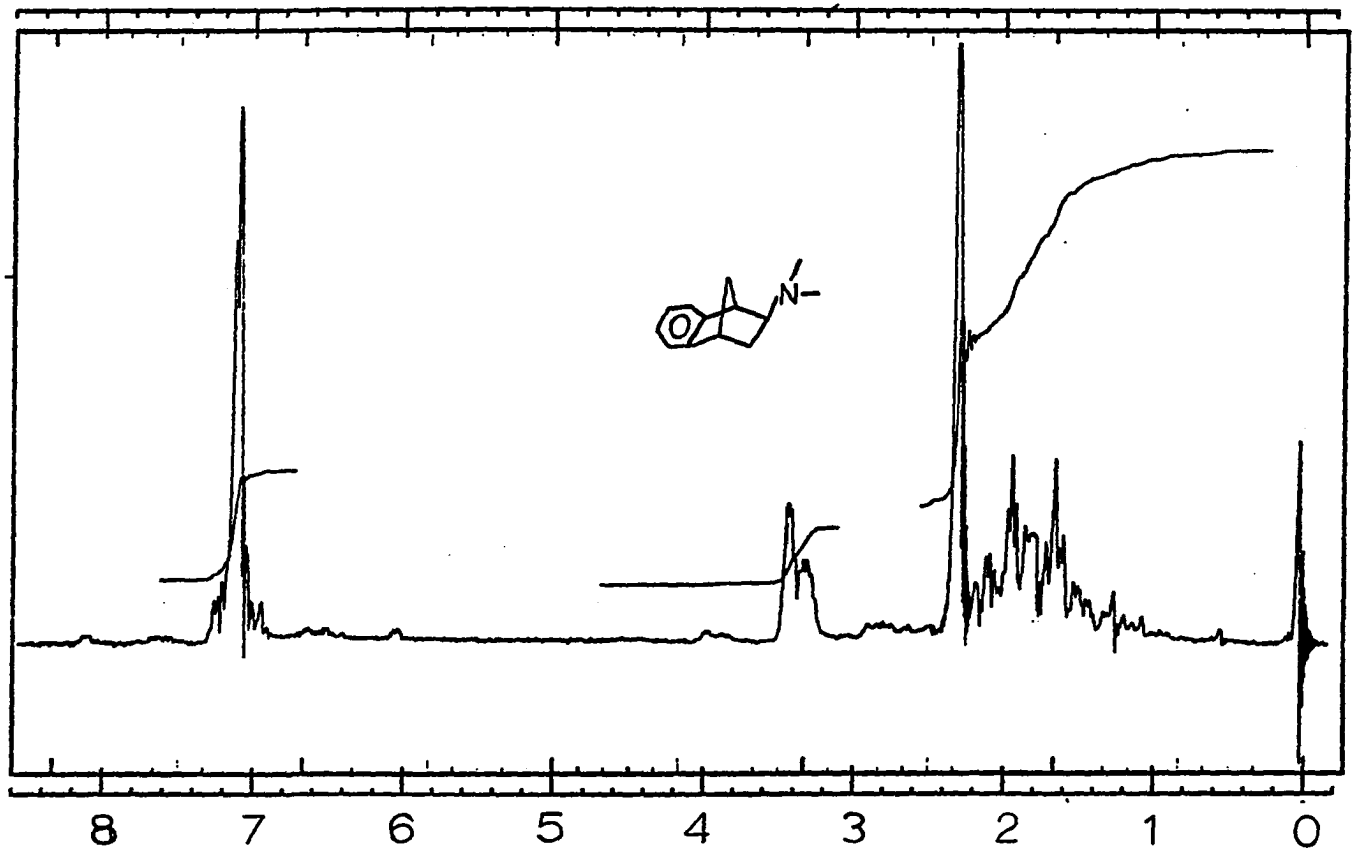


Figure 7. 60 Mhz proton nmr proton spectrum of VII, $CDCl_3$

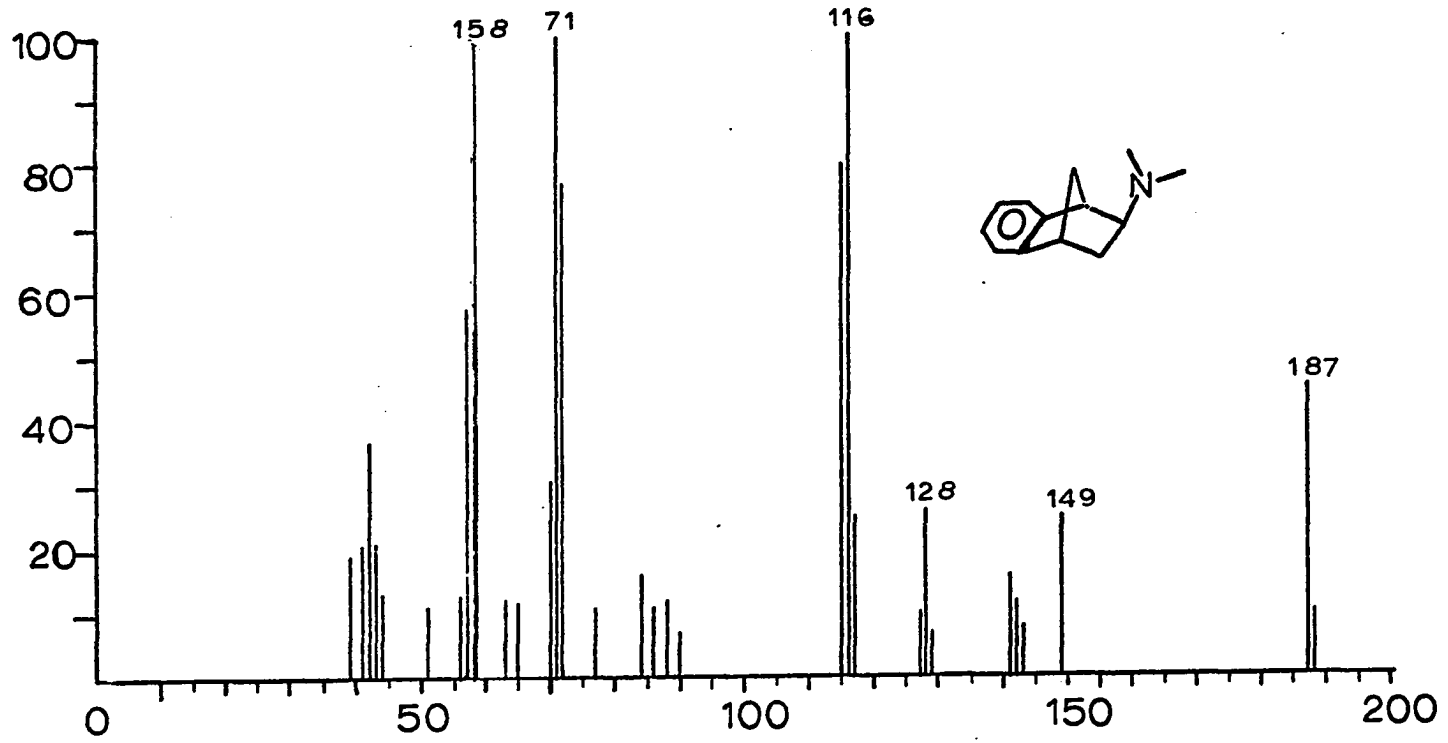


Figure 8. 70 eV mass spectrum of VII

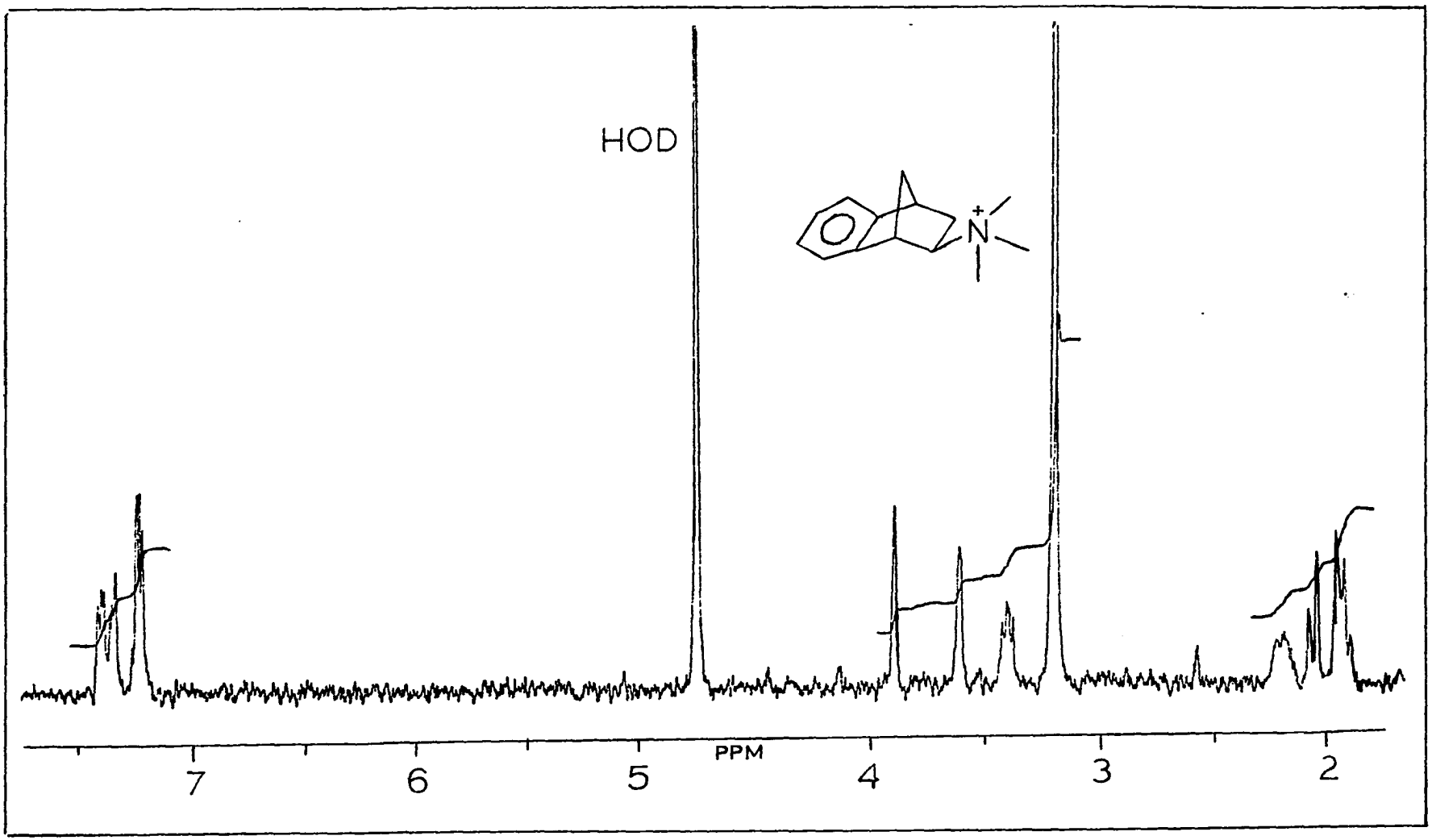
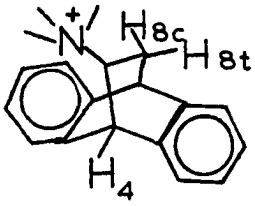


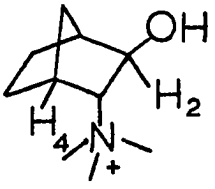
Figure 9. 300 MHz proton nmr spectrum of III, D_2O

RESULTS

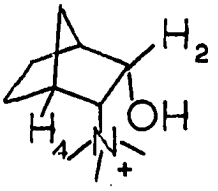
The observed $^{3}J_{N-H}$ values in systems I-V are shown in Table I. included in the table for comparison is data on compounds VIII-X[1], 3 amino acids,[27] and an alkyl isocyanide.[28]



VIII



IX



X

Tori et al[1] observed an angular dependence for $^{3}J_{N-H}$; however, their results were restricted to 0, 60, 79, and 120°. Furthermore the complications introduced via electronegativity effects of the C_2 hydroxyl groups in IX and X were recognized but could not be accounted for quantatatively. The angular dependence of $^{3}J^{15}_{N-H}$ for amino acids was observed by Lichter and Roberts,[27] but was limted to Ø=60° and

TABLE I

Compound, proton		Ø Degrees	$^3J_{NH}$ (Hz)
I	H_{5n}	150°	3.0
	H_{5x}	90	0
II	H_1	180	3.5
	H_{7x}	90°	0
	H_{7n}	150°	2.5
IIIa	H_{4e}	60	0.5
	H_{4a}	180	3.0
IIIb	H_{4a}	174	3.6
	H_{4e}	54	0.7
IIIc	H_{4a}	174	3.55
	H_{4e}	54°	0.5
IIId	H_{4a}	174	3.4
	H_{4e}	54	0.5
IV	H_4	30	$\leq$0.3
	H_{6x}	0	2.8
	H_{6n}	120	0.8
V	H_{4a}	54	$\leq$0.9
	H_{4e}	66	$\leq$0.7
VIII[a]	H_{8c}	0	2.7
	H_4	60	$\leq$0.3
IX[a]	H_4	79	0
X[a]	H_2	120	$\leq$0.3
	H_4	79	0
alanine)[b]		60 (gauche)	1.3
phenyl alanine)		180 (trans)	3.6
aspartic acid)			
2,2-dimethylbutyl)[c]		60 (gauche)	1.5
isocyanide)		180 (trans)	7

a) ref. 1
b) ref 27
c) ref 28

180°. The values were obtained for ^{15}N but when corrected by (J_{15}/J_{14}) =1.403 yielded results similar to ours. Bothner-By and Cox[28] observed the same type of angular dependence for $^{3}J_{N-H}$ in alkyl isocyanides (values at Ø=60 and 180°); however, for the given angles the alkyl isocyanides yielded $^{3}J_{N-H}$ values which were larger than those for the corresponding quaternary ammonium salts. The differences between $^{3}J_{(NR_4^+)}$ and $^{3}J_{(C\equiv N-R)}$ might be explained in terms of the different hybridizations of the nitrogen nuclei (considerably more "s" character in the isocyanides). Althought the data is very limited, the same trend (increasing |J| for increasing "s" character in heteroatom) is observed in $^{1}J_{^{13}C-H}$[29,30], $^{3}J_{^{13}C^{13}C}$[31], $^{1}J_{^{15}N-H}$[32-33] and $^{1}J_{N-N}$[34].

A plot of $^{3}J_{N-H}$ vs. Ø is presented in Fig. 10.[38] Included in this plot is the data from the results of this work (compounds I-V) and Tori's[1] data (compounds VIII-X).

A clear minimum occurs at Ø=90° and a maximum at Ø=180°. Where as previous work suggested Karplus-type relationships for $^{3}J_{N-H}$, each taken separately suffered from limited data and/or complications due to electronegative substituents. If one considers only the data for compounds I, II, and IV (8 data points, with angle Ø varying from 0 to 180°) our results clearly reveal a Karplus-type relationship between $^{3}J_{N-H}$ and angle Ø. Small deviations from the least squares plot in figure ten are best explained by differences between our assumed bond angles and the actual bond angles. One other factor which might affect our results is the presence of adjacent electronegative substiuents. For coupling constants which are <u>positive</u> as is $^{3}J_{N-H}$ a nearby electro-

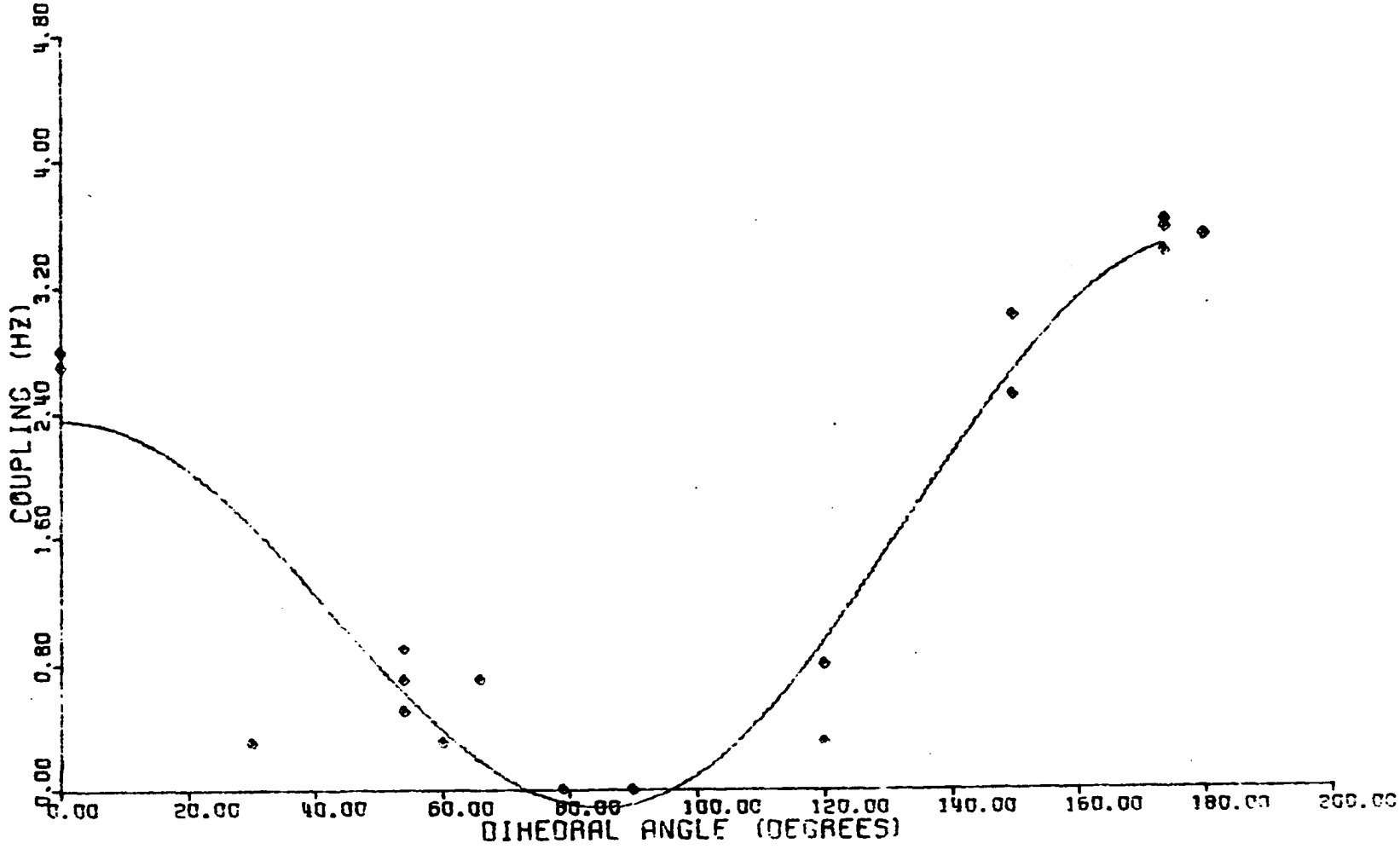


Figure 10. Plot of $^{3}J_{N-H}$ versus angle ϕ for I-III and VIII-X.

negative substitutent will <u>decrease</u> ^{3}J.[35-37] Our results from compounds III and V, with oxygen α to the observed proton, should represent minimal coupling constants.

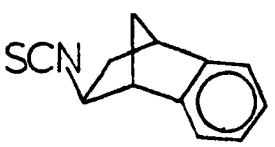
SUMMARY

In this section, we have presented the syntheses of several bicyclic quaternary ammonium salts, examined their normal and nitrogen decoupled pmr spectra, and shown that a plot of $^{3}J_{14_{N-H}}$ versus the dihedral angle ϕ clearly obeys a Karplus-type relationship. Furthermore, small differences between our data and that of others[1,27,28] can be explained by variations in the assumed bond angles and electronegativity effects. The most notable difference is $^{3}J_{14_{N-H}}$ for ϕ=180°. Tori's estimate[1] of J_{180}=5-6 Hz is too high when compared to our observed J_{180}=3.5 Hz.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR specta were recorded on a Beckman IR-8 infrared spectrophotometer. Mass spectra were recorded on a Hitachi-Perkin Elmer RMU-7E Mass Spectrometer operated at 70 eV. Nmr spectra were recorded on Varian T-60 (60 MHz) and Varian XL-100 (100 MHz) spectrometers. 300 MHz nmr spectra were provided by Professor Marc Anteunius, Laboratorium voor Organische Chemie, Rijksuniversiteit Gent (Belgium).

1,2,3,4-Tetrahydro-1,4-Methano-2-exo-Isothiocyanate (VI)

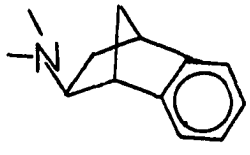


Benzonorbornadiene,[23] (1 g, 7 mmoles) was dissolved in benzene (20 ml). To this was added 50% aqueous H_2SO_4 (2 ml) and potassium isothiocyanate (1 g, 10 mmoles). After 2 hours at room temperature, an additional gram of KSCN and 50% H_2SO_4 (2 ml) were added. The mixture was then heated to reflux for one hour. On cooling, the mixture was diluted with water (50 ml) and extracted with chloroform (2x50 ml). This was washed with a saturated solution of sodium bicarbonate (50 ml), then water (50 ml). After drying over sodium sulfate and concentration, microdistillation (50-60°, 0.1 torr) yielded VI (1.18 g, 84%) as a colorless liquid, which on standing for several days, slowly crystallized. Recrystallization from Et_2O/pentane yielded colorless plates mp 35.5-36.0°.

Analysis for $C_{12}H_{11}NS$: calculated C 71.60, H 5.51; found C 71.65, H 5.69

60 MHz nmr spectrum of VI ($CDCl_3$): δ 1.85-2.2 (complex multiplet, 4H, H_7-syn, H_7-anti, and 3-exo and endo protons), δ 3.4-3.8 (complex multiplet, 3H, H_1, H_4, and 2-endo protons), δ 7.14 (singlet, 4H, aromatic ring protons). IR (KBr pellet), cm^{-1}: 2980 (m, C-H), 2100 (s, br, -N=C=S) 1460 (m, C-N), 1320 (m, C=S), 750 (sh, 1,2-disubstituted aromatic ring). 70 eV mass spectrum: m/e 201 (molecular ion), 142, 128, 116 (base peak), 102, 89, 63, 39.

1,2,3,4-Tetrahydro-1,4-Methanonaphthalen-exo-2-N,N-dimethylamine (VII)



An ether solution of the isothiocyanate (1.5 g, 7.46 mmoles) was added dropwise to lithium aluminum hydride (0.354 g, 9.33 mmoles) in ether (50 ml). After refluxing gently for 3 hours, more lithium aluminum hydride (0.15 g, 4.15 mmoles) was added, followed by addition of ethyl formate (0.75 g, 10 mmoles). Refluxing was recontinued for 8 hours. On cooling, the reaction was quenched with water (0.5 ml), 10% aqueous sodium hydroxide (0.5 ml), and finally water (1.5 ml). After filtration of the aluminum salts, the solution was dried over sodium sulfate and concentrated. Microdistillation (60-70°, 0.1 torr) afforded the dimethyl amine (VII) as a colorless liquid (0.65 g, 47%).

100 MHz nmr, ($CDCl_3$); δ 1.3-1.75 (complex multiplet, 2H, 3-exo and endo protons), δ 1.96 and δ 2.06 (multiplets, 2H, 7-syn and 7-anti protons), δ 2.3 (singlet, 6H, N-$(CH_3)_2$), δ 3.28 (multiplet, 1H, H_4-(bridgehead) proton), δ 4.02 (multiplet, 1H, H_1-(bridgehead) proton), δ 7.1 (multiplet,

4H, aromatic ring protons).

70 eV mass spectrum: m/e 187 (molecular ion), 149, 128, 116 (base peak), 71, 58, 42.

IR (film), cm^{-1}: 2980 (w, C-H), 1430 (w, C-N), 750 (sh, 1, 2-disubstituted aromatic ring).

Compound VII was further characterized at its picrate. Addition of VII to a saturated solution of picric acid in 95% ethanol immediately precipitated the salt. Recrystallization from 95% ethanol afforded VII-picrate as yellow needles, mp 137-138°.

Analysis for $C_{19}H_{20}N_4O_7$: Calculated, C 54.81, H 4.80; found, C 55.12, H 4.98.

Quaternary Methiodides I, II and IV.

Preparation of these quaternary ammonium iodides was accomplished by addition of the appropriate free base to a chloroform solution of excess MeI. The precipatated salts were filtered, vacuum dried, and then used without further purification.

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38. The computer program for the least squares analysis and subsequent plot were kindly provided by Dr. Eric Enwall, to whom we are grateful.